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LECTURES

ON

GENERAL PATHOLOGY.

A HANDBOOK FOR PRACTITIONERS AND STUDENTS.

BY

JULIUS Friedrich COHNHEIM, 1839-1884

ORDINARY PROFESSOR OF GENERAL PATHOLOGY AND PATHOLOGICAL ANATOMY IN THE UNIVERSITY OF LEIPSIG.

TRANSLATED FROM THE SECOND GERMAN EDITION

BY

ALEXANDER B. McKEE, M.B.Dub.,

CURATOR OF THE MUSEUMS, ROYAL COLLEGE OF SURGEONS IN IRELAND.

WITH MEMOIR BY THE TRANSLATOR.

SECTION I.

THE PATHOLOGY OF THE CIRCULATION.

LONDON:
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1889.

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PRINTED BY ADLARD AND SON, BARTHOLOMEW CLOSE.

TRANSLATOR'S PREFACE.

By this translation of the 'Lectures on General Pathology,' the chief fruit of a life, short in years, but unwearying in its devotion to science, becomes accessible to the English reader. Every chapter bears the mark of the author's distinctive genius; and no book, perhaps, of recent years has exerted a stronger influence on current modes of thinking in pathology. The volume now issued deals with that portion of the science with which the name of Cohnheim will always be associated—'The Pathology of the Circulation.' The translator has endeavoured to the best of his ability to faithfully reproduce the original; he has never hesitated to sacrifice elegance of expression where an exact rendering of the turn of thought seemed to him to demand it. Cohnheim himself was no lover of rhetoric; his style of lecturing was simple, often conversational; and he wrote as he spoke. The little biographical sketch is mainly taken from the "Lebensbild Cohnheim's" by W. Kühne, prefixed to the 'Gesammelte Abhandlungen,' where a complete list of the writings of Cohnheim and of his pupils will also be found.

ALEXANDER B. McKEE.

PREFACE TO THE FIRST EDITION.

The form of Lectures has been chosen for this book in the belief that when treating of a science, the development of whose various sections is disproportionate in the extreme, it is advisable to select a mode of composition which allows the author the greatest possible amount of liberty. The reader is referred to the introduction for the plan followed, and line of thought adopted in the work. I merely wish to indicate here, in a few words, the principles which have guided me in compiling the references. It was far from my intention to give an even approximately complete register of the literature. Besides referring to appropriate sections of the existing compendiums and hand-books of our science made use of by me, I have striven to cite all original researches when dealing with the questions upon which they bear. It was next my endeavour to notice more particularly the most recent literature, so as to afford the reader an opportunity of readily becoming acquainted with the present state of our science. In controversial questions especially, I have aimed to the best of my ability at a just treatment of the several views. Among other papers, I have given the preference to such as contain copious references.

INTERLAKEN; *August*, 1877.

PREFACE TO THE SECOND EDITION.

I HAVE sought in this, the second edition, to incorporate as fully as possible in the work the recent results of research, which, particularly in our science, has been very active in every direction. The plan and method of presentation has therefore remained throughout as before; yet whoever takes the trouble to compare the two editions will nowhere miss the altering and I hope improving hand. Indeed, perhaps no chapter has remained entirely unchanged; still it may be well that I should here specify those which have undergone the most considerable alterations. In the first section, the first chapter has been completely rewritten on the basis of new experiments not published elsewhere; then Chapters IV and V, which treat of Thrombosis and of Inflammation, have been in part extensively altered and in part supplemented; lastly Chapters VII, X, and particularly IX, depart considerably from the account given in the first edition. In the second section the principal changes occur in Chapter I and still more in Chapter VI; both of these have been completely recast in preparing this edition.

COHNHEIM.

LEIPZIG; *January*, 1882.

MEMOIR.

Julius Friedrich Cohnheim was born on the 20th of July, 1839, in the little town of Demmin in Pomerania. Here he received his elementary education, and in 1852 entered the gymnasium at Prenzlau, where he remained till his eighteenth year. In the autumn of 1856 he removed to Berlin, and commenced the study of Medicine.

Of his school-days and early years in Berlin, Cohnheim never cared to speak, even with his most intimate friends. His youth was cramped by the pressure of straightened circumstances. When a boy of fifteen, his father had been compelled by his affairs to leave home for Australia, where misfortunes crowded thick upon him, and whence he returned only to die in the arms of his son. Like so many eminent men, it was to the self-sacrificing devotion of an intelligent and energetic mother that Cohnheim owed his early training.

After passing his previous examination, he exchanged Berlin for Würzburg. In Berlin he had lived in the house of a relative, but now he was to enjoy that free, happy, careless student life, which comes with such refreshing novelty to the youth of Germany after the strict and arduous discipline of the gymnasium. Here he became acquainted with Hermann Immermann, who describes him as a bright and jovial student, full of drollery, and gifted with an extraordinary power of telling a good story well. These were popular qualities, but amusement was never allowed to interfere with study. After a late evening Cohnheim was often up again at five, busy with his microscope in his room, and became an ardent histologist under the influence of his teacher Kölliker.

At Würzburg, Cohnheim remained till Easter, 1860, and after spending a summer-semester at Greifswald, once more betook himself to Berlin. Here he passed his examination for the degree of Doctor, but the Thesis still remained to be written, and Cohnheim began in January, 1861, to work, under Virchow's guidance, in the Pathological Institute of the Charité. The Dissertation, "De pyogenesi in tunicis serosis," published with some additions in the 'Archiv,' is chiefly of interest as showing how early Cohnheim's attention was directed to the study of inflammation by his great master, Virchow.

At this period the Pathological Institute of Berlin was the centre of the most intense intellectual activity. From every part of Germany, and, indeed, from almost every civilised country, earnest and talented students gathered around the chair of Virchow, and carried home with them some of that keen spirit of scientific inquiry which so distinguished the teacher. It is related that some who had come under the spell used to say to the student starting for Berlin, "Unhappy man, you too are going to be infected!" Von Recklinghausen and Klebs were at that time Virchow's assistants, and it was probably as the result of his intercourse with them that Cohnheim formed the resolution of devoting his life to science. This was at once a proof of a courageous spirit and of no small love for scientific pursuits, for at no period of his life were his means of livelihood scantier. In May, 1862, his father returned with a fatal illness from Australia. Cohnheim hurried to Hamburg to meet him, accompanied him to Berlin, and tended him till his death in July of the same year. It became more than ever necessary that the eldest son should contribute to the support of his family.

But he held it unmanly to complain, and, far from bewailing his own lot, became the confidant of others, and, so far as he could, helped those whose position was but little worse than his own. With wonderful courage and self-control, he determined to employ every moment of that leisure which he feared might not long be his. He was constantly occupied in the practice of normal and morbid histology, and in gaining an acquaintance with the methods of chemical investigation. A paper on sugar-forming ferments was one of the results of this study.

About this time Cohnheim was brought into close contact with the great physician, Ludwig Traube, to whose memory the 'Lectures' were dedicated. Knowing that he might ultimately be compelled to practise, he seized the opportunity afforded in Traube's clinic of fixing and widening his clinical knowledge, but sought chiefly to familiarise himself with the physiological and experimental methods of which Traube was a master. So impressed was he by Traube, and so habituated to his mode of thinking, that, except Virchow, Traube must be regarded as having done more to influence the life-work of Cohnheim than any other.

The one serious interruption to Cohnheim's study at the Charité was now to take place. In the German-Danish war of 1864 he served as surgeon with the Prussian army. It was in Schleswig-Holstein, after the death of his younger brother, Albert, who fell shot through the head in the victorious passage to Alsen, that Cohnheim, surrounded by sympathising friends, embraced the Christian faith. Being now the sole support of his mother, he was released from service, and the post of assistant in the Pathological Institute, vacated by von Recklinghausen on his call to Königsberg, was given him by Virchow. By this event his future was determined.

The few years spent as assistant were a period of unwearying labour. Busied with the ordinary work incidental to his office, he yet found time not merely for original investigation, but for teaching; by which he was enabled to live himself, and to aid in the support of his family. Several minor contributions appeared in the 'Archiv' in rapid succession. Then came the researches on the structure of striped muscle-fibre and the nerve-terminations in muscle, in both of which he used the silver method introduced by von Recklinghausen. These were followed by an important investigation into the pathological anatomy of trichinosis. Some idea of his extraordinary productiveness may be got from the fact that in 1867, besides minor contributions, there appeared in the 'Archiv' the papers "On the Terminations of the Sensory Nerves in the Cornea," in which he made known his gold method; "On Tuberculosis of the Choroid;" "On Inflammation and Suppuration;" and "On Mechanical Hyperæmia."

By the investigation into the inflammatory process, the fame of its author was secured. Von Recklinghausen had already discovered that granular pigment is taken up by the leucocytes in the circulating blood, and had found the "wandering cells" in the lymph-spaces of the connective tissue. These discoveries prepared the way for the investigations of Cohnheim. Virchow had said that no difference exists between white blood-cells and pus-corpuscles. Cohnheim now announced their identity—that the pus, with the cells contained in it, is derived from the blood. The observations of Addison and Waller had been forgotten; it was reserved for Cohnheim to independently establish the diapedesis of the blood-corpuscles beyond all possibility of doubt, and on this basis to found his theory of inflammation.

During the following year Cohnheim was occupied, in conjunction with Bernhard Fränkel, with an inquiry into the communicability of tuberculosis to animals. A call to Amsterdam was declined, as there was an immediate prospect of the Chair of Pathology at Kiel, where, during the war, he had made many friends. Here we find him in the following autumn, now twenty-nine years of age, busied with the preparation of his lectures, somewhat troubled by the business cares of his office, and a little regretful at the loss of the larger life of Berlin. Still he found time to resume the study of the circulation; and, having already investigated the effects of venous obstruction, now turned his attention to the subject of embolism, for which Virchow had laid the foundation. The varying results of arterial obstruction were referred by Cohnheim to the anatomical disposition of the vessels, *i. e.* to the presence or absence of an adequate collateral circulation beyond the seat of obstruction. The objections raised to his theory of inflammation called forth the paper on the behaviour of the connective-tissue corpuscles in inflammation. That Cohnheim spared no pains to arm himself at all points for his particular field of inquiry may be gathered from the circumstance that he devoted two months of 1869 to the study of the circulation as a learner in Ludwig's laboratory.

During the winter of 1870–71, while the armies of Germany were investing Paris, Cohnheim acted as prosector to the military hospitals in Berlin.

In the following summer he renewed an old acquaintanceship with Martha Lewald, to whom he was united on the 20th of May, 1872. This was a happy marriage, to which Cohnheim owed much,—sympathy with his aims and labours, and untiring devotion during years of sickness.

The autumn of the same year saw another event of no small importance—Cohnheim's removal to Breslau. Many pleasant companionships had to be given up; but his personality was one that quickly inspired friendship, and in Breslau he was soon on a footing of intimacy with many of his colleagues, among whom the great physiologist, R. Heidenhain, was perhaps the most sympathetic.

It was at the beginning of his career at Breslau, that the symptoms of gout, which had already appeared in Kiel, first assumed serious proportions. He was compelled to spend the entire winter 1873–74 in Montreux, but returned much invigorated, and, as he thought, cured. He now exerted himself to obtain a suitable Pathological Institute; and in it he had for the first time a field for labour commensurate with his energy and capacity. He soon drew students around him, to many of whom he could entrust particular subjects of investigation, he checking the results, or himself going to work with them even to the minutest details. Thus he multiplied time, eyes, and hands; and trained up his students for independent research. The publications appearing exclusively under his own name during this period were few, but no one acquainted with the work of Senftleben, Lassar, Litten, B. Heidenhain, &c., can doubt from what source they drew their inspiration. While at Breslau, the observation of a case of congenital myo-sarcoma of the kidneys first led him to the conception of the embryonic theory of tumours; and here too it was that his views as to the communicability of tuberculosis underwent a transformation. With Salomonsen, of Copenhagen, he introduced particles of tubercular material into the anterior chamber of the eye, and, the suppuration and inspissation of the pus usually complicating inoculation in other parts being here absent, he was able to trace the development of the tubercles to their proper source.

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In November, 1875, Cohnheim met Robert Koch. The now celebrated bacteriologist was then a country practitioner, and came to Breslau to submit to Cohn his cultivations of anthrax-bacilli. Cohn, who had had many sad experiences with alleged pure cultivations of pathogenic micro-organisms, was at first inclined to treat Koch's discoveries with distrust, but on seeing the preparations, he sent to the Pathological Institute with the request that someone should come over at once, as the matter was important and highly interesting. As Weigert was just about to make a post-mortem, Cohnheim himself went over, and on his return said to his assistant: "Now leave everything as it is, and go to Koch. This man has made a magnificent discovery, which, for simplicity and the precision of the methods employed, is all the more deserving of admiration, as Koch was shut off from all scientific associations. He has done everything of himself and with absolute completeness. There is nothing more to be done. I regard this as the greatest discovery in this domain, and believe that Koch will again surprise and put us all to shame by further discoveries." By this meeting, Cohnheim's belief in the organised nature of the virus of the infective diseases was confirmed; and it was a great gratification to him to have lived to see Koch's discoveries of the bacilli of tubercle and cholera.

Two sons were born to him in Breslau. "Those who were on terms of intimacy with him," says Kühne, "know what happiness filled his home, what perfect harmony and rare sensibility pervaded it, what abundant self-sacrificing love." During the periods of enforced leisure, which even in Breslau became more frequent, he was sustained by the tender ministrations of his wife, who never tired of reading to him, and it was the ample and varied field of literature thus travelled over, which—together with the companionship of professors in the other faculties, notably the brilliant and learned Lujo Brentano—supplied Cohnheim with that general culture, somewhat despised by him in his earlier years.

Exaggerated reports of his illness wrecked the plans of those who wished to secure him for the Chair at Vienna, vacant by Rokitansky's death. But early in 1878 came the call to Leipzig. He accepted it without hesitation, regarding it as the attainment of a great goal. Here the second volume of the 'Lectures' was written, and new investigations into the pathology of the circulation were undertaken. With von Schulthess-Rechberg, he examined the effects of occlusion of a branch of the coronaries of the heart; and with Charles Roy, studied the circulation in the kidneys. This was the last publication superintended by Cohnheim himself.

At the close of the first summer-semester (1878) Cohnheim felt compelled to seriously attempt the cure of his disease, and selected Carlsbad. Still the attacks of gout became more and more frequent, and the periods of enforced rest longer. At length, after the exertions of the summer 1883, he felt too weak to think of lecturing during the following winter-semester. He returned from Constance, where he had spent part of the vacation, only to fall ill immediately. Still he did what he could; and even after he became permanently confined to his room, sought through his friends to keep in touch with the investigations carried on in the Institute. The assistants and students were allowed to submit their results to him in his house. Here his friends gathered round him; and his chamber became the centre of a lively social intercourse.

In the Easter vacation 1884, he once more sought strength in Wiesbaden; and on his return, despite every warning, attempted to resume his lectures. As he could not mount the steps, he was carried into the theatre. But his strength failed him. He grew gradually feebler during the following months; and died in the early morning of August 15th, 1884, suddenly, and without a struggle.

He lies in the *Friedhof* at Leipzig, in the part reserved for the University, where a noble monument, the work of R. Siemering, has been raised to his memory by friends and disciples. It represents with poetic freedom, and with wonderful pathos, the sudden termination of his two-fold life.

This is not the place to discuss his merits as a pathologist. Of his methods and mode of thought the reader of the following pages will have ample opportunity for judging.

CONTENTS.

PAGE
Translator's Preface v
Preface to the First Edition . . . vii
Preface to the Second Edition . . . viii
Memoir of the Author ix

INTRODUCTION . . 1

SECTION I.

THE PATHOLOGY OF THE CIRCULATION 17

CHAPTER I.

The Heart . . . . . . 19—92

CHAPTER II.

Changes in the total Peripheral Resistance . . 93—108

CHAPTER III.

Local Disturbances of the Circulation . 109—171
    1. Local Anæmia . . . . 116—133
        Active Hyperæmia . . . . 134—144
            [illegible]ive Hyperæmia . . . . 144—171

PAGE

CHAPTER IV.

THROMBOSIS AND EMBOLISM . . . . 172—241

CHAPTER V.

INFLAMMATION . . . . . 242—382

CHAPTER VI.

HÆMORRHAGE . . . . . 383—412

CHAPTER VII.

PLETHORA AND ANÆMIA . . . . 413—446

CHAPTER VIII.

HYDRÆMIA AND ANHYDRÆMIA . . . . 447—467

CHAPTER IX.

CHRONIC ANÆMIAS . . . . . 468—501

CHAPTER X.

PATHOLOGY OF THE LYMPH-STREAM. DROPSY . . 502—528

CORRIGENDA.

Page 126, 11 lines from bottom, *omit* places.
„ 223, 18 „ top, *for* features *read* fractures.
„ 299, 18 „ top, *for* trichini *read* trichinæ.
„ 333, 16 „ bottom, *for* statified *read* stratified.

LECTURES ON GENERAL PATHOLOGY.

INTRODUCTION.

DEFINITION OF THE NOTION OF DISEASE. OBJECT, PROGRESS, AND METHODS OF GENERAL PATHOLOGY.

THAT pathology is the science of disease, while physiology seeks to ascertain the laws of health, is so familiar to all of you that it may appear superfluous to define more precisely the task which we set ourselves in this course of lectures. Yet you may perhaps meet with some difficulty on attempting an exact definition of the expressions "ill," "disease," "diseased," which you nevertheless make use of daily. A negative definition is commonly resorted to, and "ill" is conceived as meaning simply the contrary of "healthy." But what do we include under the conception "health"? Biological science teaches that in a number of individuals the same organs recur in precisely the same number, form, size, and chemical constitution; and we call the sum of the individuals so constituted, as you know, a species. It is this arrangement and constitution which we designate the type or normal type of the species, within which there may yet exist certain individual variations. These variations form, it is true, deviations from the specific type; yet, when inconsiderable details are concerned, we neglect them, and are accustomed, among such variations, to regard as normal that *modus* which recurs most frequently in a given large number of individuals. On the other hand, every considerable deviation from this type we name a malformation. Perhaps I need hardly point out that the maintenance of the type in point of sex, as well as of age and development, is necessary to the preservation of the normal standard. Developed mammæ, normal in a woman, are abnormal in a man, and, on the other hand, the beard is abnormal in a woman. Undeveloped genitals are typical in a child, abnormal in an adult; and a thymus or a pervious ductus arteriosus, which are normal in the new-born, would constitute a malformation in youth. These points of view being kept in mind, experience shows that among the individuals comprised in a species, in our case among human beings, there are some who present considerable deviations from the human type, and are therefore, in some respect or other, abnormal.

Now, all these malformations belong unquestionably to the domain of pathology, taken in the widest sense, and are in fact minutely treated of in works on pathological anatomy. Nevertheless we are not in the habit of calling the absence of a kidney, the presence of a harelip, or of a double vagina a disease. We call such a condition an anomaly, a deformity, even when not congenital but acquired; as in the case, for example, of a cicatrix, or where an extremity is missing after amputation, or the foreskin after circumcision. We speak of disease only when we have an *occurring*, a *progression*, a *process* in mind; and, just as we bring the anomalies above mentioned into immediate relation to the descriptive natural science of man, or anatomy in a broader sense, we connect disease with physiology. The dead body may be deformed, anomalous, but never ill, just as there is an anatomy of the cadaver, but no physiology. And, so completely is the notion of disease inseparable from life, that in the sciences of inanimate nature the expressions "normal" and "abnormal" are very frequently employed, the terms "healthy" and "diseased" never.

This consideration, it is evident, leads us logically to define disease as a "*deviation from the normal or healthy vital processes.*" But if, as we found when speaking of malformations, a certain degree of divergence from the type must be present in order that they may be at all regarded as such, this applies with still greater force, and indeed properly only in the case of diseases. For, while the
of anatomical structure varies only in certain subo

particulars, so that, for example, in individuals of the same age and sex, certain muscles or bones are wont to differ at most in point of size and weight, the course of the vital processes in different persons is well known to be subject to variations of incomparably greater extent. The reason of this is evident. The healthy organs and their mechanisms always remain the same, and the laws of their operation continue absolutely the same, but the conditions which act upon them, and in which they perform their functions, vary. It is due solely to the variation of these conditions that the same perfectly healthy individual produces at one time much, at another little, carbonic acid; urinates or perspires now little, now much; sleeps much or little; that the frequency of his pulse rises at one period, at another falls; that the temperature of his skin varies within wide limits, and so on; and when one recalls the truly immense differences in diet, external temperature, occupation and manner of life, residence and character of soil to which human beings are exposed, one cannot but be amazed that the organism is capable of maintaining its health despite these differences. This is achieved because our body has the capacity of accommodating itself to, or overcoming, the most various external conditions, so that these shall not disturb the regularity of the vital processes; and this it effects by the most ingenious and delicate arrangements, new examples of which are daily brought to light in the progress of science. If the external temperature be high, the vessels of the skin dilate, and there is a plentiful secretion of sweat with evaporation; if it be low, the contraction of the same vessels limits the radiation of heat; if much water be introduced into the blood by drinking, a large quantity of urine will be secreted; if the blood be deprived of a large amount of water by sweating, the urinary secretion is reduced in the extreme; and, on the increased production of carbonic acid during muscular exertion, there follows a rise in the excretion of carbonic acid through the lungs. Examples might be thus accumulated *ad infinitum*, and to take an instance, hardly any study is more attractive than the manifold contrivances for regulating the cardiac activity and the flow of the blood, with which we have become acquainted in recent years. But even the experience of daily life shows how much the organism is capable of accomplishing in this respect. Amongst our beverages, &c., are many which in small quantities are harmless, but in larger decidedly injurious, or, as we express it, poisonous. Who does not know that the same dose of alcohol or tobacco which disturbs the physiological equilibrium of the unhabituated, *i. e.* causes illness, is to the habituated completely indifferent? Now, it is self-evident that the direct action of the same quantity of alcohol will always be the same on the same individual; otherwise we should not have physiological laws to deal with. But the regulative, compensatory capabilities of the organism have been gradually aroused and disciplined, and they now cause the dose of alcohol to be no longer a poison to the individual. Of course this takes effect only within certain limits, beyond which the poison, as everyone knows, asserts itself anew as such, and becomes an exciter of disease. This illustration, however trivial it may seem, may yet serve as starting-point for a more accurate paraphrase of what we call disease. We speak of a disease *where the regulative mechanisms, acting in opposition to one or more vital conditions, are no longer adequate to secure that the various vital processes shall proceed undisturbed.* Now, it is self-evident that these reflex mechanisms are present, and perform their functions similarly in all persons—yet they are far from doing so with equal energy, with the same quantitative functional capacity. Hence it will be understood without further explanation that one individual may be better able than another to adapt himself to one and the same external condition; or, in other words, that disease may be produced in one person by causes which have no effect on another. Disease is nothing more or less than a deviation from the normal vital process, brought about by the action of external conditions and the reaction of what may be called in general terms the internal regulative capabilities of the organism. The extent of the deviation, or the severity and duration of the disease, results, on the one hand, from the intensity of the influences exerted by the former, *i. e.* from the degree in which the external conditions are heterogeneous and uncommon, and, on the other hand, from the functional power of the latter. I need hardly mention that enormous differences are presented by disease in point of severity and duration, for you are all aware that very brief and very prolonged illnesses, as well as all possible gradations between the two, exist; and you know too that diseases of all imaginable degrees of intensity occur, some of such trifling character that they may be spoken of as mere indisposition, and others endangering life itself.

The conception of the nature of disease here expounded is quite modern, and came to be recognised only in the course of this century. Should this surprise you, considering the apparent simplicity of the matter involved, you will please remember that in all natural sciences the direction has been, and must have been, from the special to the general. Just as in botany an oak or a pine were known to us before we had proceeded so far as to deduce and determine the conception "tree," and still more "plant," so also in pathology. We never meet with an individual, who is merely in general ill, but only with such, it is evident, who suffer from one or more particular diseases—even though we are not always in a position to recognise them. The diagnosis of a disease is analogous to the determination of the species of a plant. Thus in accordance with a natural necessity, the knowledge of individual maladies has advanced far more rapidly than the recognition of the conception, disease; or rather, it was necessary to be acquainted with a large number of individual maladies before a clear definition of the nature of disease could be formulated. The progress of pathology is historically this: the recognition of a multitude of individual diseases or special pathology preceded the doctrine of disease or general pathology, and the latter has arisen only on the foundation of the former. That this was the only pathway leading to the goal is most clearly proved by the numerous and often fantastic attempts of general pathology in former centuries, before the empirical material, *i. e.* a knowledge of the individual diseases, was adequate thereto. Speculative systems were set up, which had of course to collapse the moment the aspect of special pathology became altered in the light of new facts.

Nothing has been more influential in this respect than

the creation of pathological anatomy, which, as you are doubtless aware, owes its existence to Morgagni. Only after experience had been gained as to the changes undergone by the individual organs in the various diseases, was it possible to build up an objective special pathology, resting on facts for its foundation. In truth the contrast between former centuries and the present one in manner of expression and mode of viewing a subject cannot be exaggerated, and a formal investigation is in every case necessary in order to determine what the older writers really meant to convey by definite names of diseases: that most secure of footholds, which the post-mortem appearances afford, was wanting. This knowledge has become so much a part of our flesh and blood, that on hearing the name of a disease, of pneumonia, for example, we recall both the symptoms which the patient presents and the condition and appearance of his lung. We regard the clinical symptoms and the anatomical changes as equally valuable factors in the estimation and determination of a form of disease. The knowledge of the symptoms gained by observation at the sick bed, and the knowledge of the anatomical changes, as revealed with but few exceptions by post-mortem examination, are alike indispensable to the understanding of a disease. Neither of them alone is sufficient, just as little as in normal physiology the most minute and accurate knowledge of the conformation and structure of a muscular fibre permits a surmise as to the contractile power of the muscle, or the most strict observation of its action, even when conjoined with a determination of its collective physical properties, allows of an approximate guess as to its structure. To pathology this applies, if possible, in a still higher degree. It is impossible, from the post-mortem appearances in a case of typhoid, to sketch a picture of the course and symptoms of this disease, having even a remote resemblance to the reality, nor—to take a chance example from the microscope—can anyone in the least deduce the characters of the urine *intra vitam* from fatty degeneration of the renal epithelium or from amyloid degeneration of the renal vessels. On the other hand, you might observ
the sick bed, making use of

examination, and it would still be absolutely impossible, in the great majority of cases, to represent to yourselves the changes in the disease before you, by way of example, to construct the picture of a tuberculous lung, typhoid intestine, or round ulcer of the stomach. This can be attained only when the observation of symptoms at the sick bed and the anatomical examination *post mortem* are made use of equally—whereby the latter must, it is evident, cover the entire of the organic changes, the chemical no less than the morphological.

What has been discovered in this purely empirical manner constitutes the subject-matter of special pathology. From it you learn, for example, that in the disease called pericarditis the patient has fever, has an abnormally large area of cardiac dulness accompanied by certain sounds, that his pulse, his urine, are of such and such characters, that his skin presents a certain colouration, &c., and that an exudation of a certain constitution is present in the pericardium. This is to some extent an accurate description of the disease in question, making it possible for you to say that a person presenting such and such symptoms during life, or in whom you find such an exudation post mortem, suffers or has suffered from pericarditis. Special pathology is, then, a *descriptive* natural science; it is evidently a corelative to that science of healthy man called anthropology in a wider sense. Anthropology embraces (1) the science of human anatomy, gross and minute; (2) the science of the so-called natural history of man, *i. e.* his manner of life, its duration, and all those activities and functions which are capable of being discovered by direct observation, as respiration, nutrition, propagation, intellectual and sensuous activity, sleep, gait, language, &c. Now, you have not in your inquiries into the healthy human being rested here, but, inspired by the desire to *apprehend* the vital processes in man, you have pushed on, and have dedicated yourselves in the most thorough fashion to the study of normal physiology, that is, to the science whose office it is to *explain* the phenomena and processes of life.

The same office which is performed for healthy man by physiology in contradistinction to anthropology is, as opposed to special pathology, the theme of the science which we designate by its traditional name, general pathology. General pathology is an explanatory science, and seeks (1) to discover the *causes of diseases*, and (2) to show the *inner connection of the phenomena of disease*. The first of these is coextensive with the doctrine of etiology, the second with what is most appropriately called morbid physiology. From the definition of disease previously propounded, according to which it is a deviation from the vital processes brought about by alteration of the normal vital conditions, it follows directly that the causes of disease are, and can be, nothing else than vital conditions, that, in other words, they are external to the organism itself. Other vital conditions are substituted for the ordinary ones, and, while the organism reacts to the latter by means of the normal vital processes, it responds to the former by means of the pathological, *i. e.* by means of disease. A disease arises the moment the deviation from the ordinary vital conditions is extensive enough to cause any perceptible disturbance of the regular vital processes, and, on the other hand, not so extensive as to result in the destruction of life, —in death itself. Accordingly you will have not merely to seek externally to the organism for the causes of all acute affections—I remind you, for example, of the traumatic and infective diseases—but must trace to the same source all chronic complaints, and all such too as are themselves again the effects transmitted by diseased stuctures present in the body. When an individual with a valvular lesion gets embolism of the brain, or dropsy of the subcutaneous areolar tissue, or albuminuria, he falls ill, it is true, in consequence of the cardiac lesion present in the organism; yet this again is only the product of an earlier, perhaps very early, illness, which must itself be finally referred to a cause, if in many cases unknown, at all events seated outside the organism. If you realise this point the extraordinary interest of the etiology of disease will at once be apparent. A thorough understanding of diseases is, of course, inconceivable without a knowledge o as the most important office of hygien can only be disc d wh upon, a certain and rational etiology. But however important is this part of general pathology, much is wanting before it can take rank as a true science. It is plain from the nature of the case that the etiology of disease possesses a well-nigh unlimited compass, and must encroach upon the most heterogeneous sciences. Cosmical physics, meteorology, and geology as well as the social sciences, chemistry as well as botany and geology,—etiology is related to all of them, and draws from them its facts. Nor can there be any doubt whatever, that with the ever-increasing complication of the vital conditions in which man lives the number of diseases has also steadily increased, so that special pathology has not merely undergone, like physiology, an increase relatively to our knowledge, but has become absolutely by far more comprehensive than it formerly was. Yet it is not the range but the nature of the subject which interferes with its scientific treatment. True, the chapter on general etiology in our modern text-books has no longer the odd appearance which it not so long ago presented, when the most heterogeneous subjects possible, from temperament to beds, from atmospheric electricity and marriage to mould and fleas, from heredity to drinks, were therein treated; but though discussions dealing with the vague and in great part hypothetical are nowadays prudently avoided, no great improvement has been effected. Please do not misunderstand me. I am the last person to dispute that these matters may be of importance for the etiology of a disease; what I deny is, only and solely, that any scientific principle whatever is in question here. Etiology can be nothing more, I believe, than an enumeration and discussion of very different factors, having only one feature in common, namely, a capacity to act as exciters of disease. With affairs in this state, it would unquestionably be of scientific advantage to hand over the minute systematic discussion of the characters of the soil and climate to general physiography, of food and drinks to physiological chemistry, of the parasitic animals and plants to zoology and botany respectively, in short, to relinquish to the different sciences what belongs to them. I am not blind to the fact that it may indeed be very desirable from a practical standpoint

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to treat at least certain sections, which would presumably be somewhat meagrely dealt with in their respective sciences, separately and *quasi*-independently. Yet it might even then be questionable whether etiology should preferably be discussed as a perfectly isolated whole, or treated of in connection with the chapters of special and general pathology to which it is directly related.

I myself shall adopt the latter course in these lectures, because I am persuaded that it is far more to your advantage to concentrate our united energies on the other branch of general pathology, namely, *morbid physiology*. This science, as its name indicates, bears the same relation to normal physiology as does morbid to normal anatomy. While in morbid anatomy we learn the modifications undergone by the morphological (or chemical) constitution of the individual organs in disease, morbid physiology teaches *how the functions of the affected organs are performed under abnormal circumstances, i.e.* subsequently to the action on the individual of conditions differing so considerably from those usually in operation as to derange the normal vital process. Bearing this in view, you will at once recognise that the subject matter of normal physiology is not sufficient for our purposes in general pathology. It is of course perfectly true that the laws of physiology fully apply to the diseased organism as well as to the healthy one; but since physiology explains the processes of healthy life alone, *i. e.* of life under ordinary conditions, it does not without more ado help us to an insight into the processes going on within the organism when the conditions are essentially changed. Nowhere does physiology afford information as to what occurs when, in addition to the ordinary food, a perfectly foreign substance, such as phosphorus, for example, is absorbed by the body. From physiology we receive the most detailed intelligence as to the normal circulation, *i. e.* where heart, vessels, and blood are healthy; but of the state of the circulation when the valves do not close in consequence of previous disease, or when the vessel walls are altered, or when the blood is coagulated in some part, we learn nothing from physiology. To suppose that it is possible to construct a morbid physiology by simply transferring the precepts of normal physiology to the sick bed is therefore an error; the problems to be answered by our science are quite independent, and here too it will be proper ourselves to set hands to the work, and by personal effort to solve the riddle presented by the complicated phenomena of disease.

Physiology is, it is true, the best and most trustworthy guide on our way, not only in matters of detail, inasmuch as we always and in every case start from it, and accept no explanation which is opposed to its doctrines, but quite specially in that it points out the direction we are to take. Just as modern physiology has long broken with all speculative systems, and become an explanatory science after the manner of physics and chemistry, so do we banish from us in pathology all the systems which have succeeded one another in large numbers in the course of centuries. Far be it from me to deny our indebtedness to these manifold systems for many a great and important advance in pathology; but they have as such, whatever be the names they bear, a purely historical interest. General pathology knows no other direction and no other classification than that which obtains in physiology, and following this science, we shall in succession treat of the pathology of the circulation, digestion, respiration, nutrition, &c.

Not merely the direction, however, but above all, the method of investigation is the same in morbid as in normal physiology. You know what the most essential aid of physiology is, that one by which she has become an inductive natural science in the sense that chemistry and physics are such; it is experiment—and where purely physical and chemical experiments are inadequate,—express physiological experiment. By experiment, as is well known, the single possible factors are tested as to their performances, and the conditions in which an organ works are varied in order to obtain information as to the significance of the individual factors. The results of physiological experiment are in the first place of service to pathology; then, however, we make use of pathological experiment, which was first practised in England by John Hunter, and in France by Magendie, yet was only raised to the rank it at present occupies as our most important fundamental aid by the researches of Traube and Virchow in the fifth decade of this century. One circumstance, as will be readily understood, makes experiment a still more pressing necessity in pathology than in physiology, namely, that we are in a very much higher degree dependent on chance for material for observation than is physiology. Normal men and animals are found at all times and in all places; it is by no means so with the diseases one desires to investigate. This dependence on contingency for material makes itself very intensely felt, even in the investigation of the anatomical side of the processes of disease. Every dead body is equally valuable so far as the anatomy of the normal lung is concerned, provided this organ has been healthy; it is otherwise with the inflamed lung. Here it is very different whether the individual has died on the second or third or as late as the eighth day; for inflammation of the lung is progressive, while anatomical examination can evidently only supply information as to the condition of the lung which prevailed at the moment of death. This gap is filled by pathological experiment. By its aid we are in a position to work out the anatomical history of many highly important processes, either following them by continuous observation, or at least subjecting them to examination at whatever intervals we please; thus our most valuable knowledge of the processes of morbid development and growth, of intoxications, of the processes of inflammation, thrombosis, and embolism, of dropsies, and of many other subjects is owing to experiment. Nor is it of less importance in the etiology of disease, which from its very nature is almost exclusively thrown upon experiment, for its really final and radical advancement. Lastly,—and this is perhaps the most beautiful office of experiment—we take advantage of it, exactly as in physiology, to ascertain the connection, interdependence, and mechanism of the processes in the various diseases. An individual with a tumour of the brain presents, amongst other symptoms, profound stupor; experiment is called in to decide whether the stupor is a consequence of increased intracranial pressure. A patient, whose urine is very small in amount, gets œdema; experiment must determine whether this is a result of the accumulation of water in the blood or not. When a large pleuritic exudation is present, the arterial blood pressure is wont to be very low; we resort to experiment to ascertain whether this lowering of pressure is owing to partial obstruction of the pulmonary blood-vessels, or to what other cause. You see, the offices of pathological experiment are numerous and important. But if, on the other hand, experimental pathology has not been carried to that stage of elaboration and perfection which its physiological sister enjoys, you will not forget that the latter is considerably the elder. Hence it may, I believe, be confidently anticipated that, after we have learned more every day to exclude the disturbing secondary effects, such as pain, excitement, &c., and to refine the experiments themselves, we shall succeed in still considerably extending and amplifying the domain of pathological experiment. True, there will always remain, and we must not hide this from ourselves, a large part of pathology, unapproachable by this method. Such in the first place are the diseases of organs so concealed as to be out of the experimenter's reach; yet this is only relative, and, in view of the performances of modern surgery, there may very soon be hardly anything inaccessible to the experimental pathologist. An insuperable difficulty, however, is presented by all the processes which are peculiar to man, and which are neither met with spontaneously, nor can be artificially produced in animals—and these, even if we leave the psychical out of account, are very numerous and important.

Under these circumstances it is of the greatest value to our science that nature, so to speak, herself presents in the various diseases a rich experimental material. When one and the same phenomenon is observed in very different affections, this is manifestly nothing more or less than a variation of the conditions, which must of course be of service in the recognition of the connection and nature of the process. Albuminuria is a symptom making its appearance in some cardiac lesions, in inflammation of the kidneys, in amyloid degeneration of the glomeruli, in pyrexia, in the second stage of cholera, and so on; what are these but variations of the conditions, and in such variety as could hardly be furnished by means of experiment? Or, to choose an illustration from a quite different domain, when a particular form of tumour appears in very various localities, in individuals of very unequal age and unlike constitution, of very dissimilar mode of life, different previous history, &c., these are all in a manner experiments instituted by nature, which we need only rightly interpret to get a clear idea of the causes, laws of growth, and significance of the tumour. Nor are these mere isolated examples; systematic and careful observation by the sick bed is a downright inexhaustible source of knowledge, and in this direction morbid physiology possesses advantages not shared by its sister science.

I have now, I believe, briefly explained the object, progress, and methods of general pathology so far as to enable you to see what you have to expect in this course of lectures. Historically our science has developed from special pathology, in the construction of which, again, clinical medicine and pathological anatomy have united. Yet it would be undesirable to allow morbid physiology to form the last stone in the edifice of your studies also. For every individual need not, indeed should not, go through the same course of development through which the entire science has passed. On the contrary, your teachers at once meet you with the accumulated possessions of science in its various departments, and a course is adopted in teaching the very reverse of that which would correspond to the historical development of the sciences. You have occupied yourselves with special pathology and with special surgery and midwifery before visiting the corresponding clinics, and the same plan will be expedient in general pathology. It is of course in the abstract undeniable that the greatest gain from the study of our science will accrue to him who has familiarised himself with disease by repeated clinical observation, but this applies in an equal degree to normal physiology, and indeed, if you will, even to normal anatomy and embryology. But as this does not concern us—you would not now be sitting on those benches had you already completed your studies—my lectures will be addressed chiefly to are commencing their clinical work. That which is indispensable as preparatory knowledge, that which we shall always take as our starting-point, is normal physiology. Further, all the knowledge you have acquired of pathological anatomy—a subject which should, properly speaking, precede morbid physiology, just as normal anatomy leads up to normal physiology—will be of essential service to you in understanding what follows. I lay less stress on a detailed knowledge of special pathology as a preparation for this course; you will, I hope, more easily make this your own after having listened to these lectures. For special pathology is, on the one hand, as it treats of symptoms, an application of morbid physiology, and, on the other, it shows how in the different diseases the various derangements of physiological function of the individual mechanisms are combined. Moreover, I do not presuppose that any one of you has already attended the clinics; on the contrary, I believe I can promise that it is precisely the pursuit of morbid physiology which forms the best preparation for, and introduction to, clinical study; you will thus be enabled to understand very much which would otherwise be simply retained by memory.

SECTION I.

THE PATHOLOGY OF THE CIRCULATION.

We shall most advantageously commence our inquiries with that section of our subject, which in the systematic study of normal physiology is usually placed first, namely, the *circulation*. In accordance with the principles we have adopted for our guidance, the pathology of the circulation is nothing more or less than an *exposition of its behaviour under pathological*, i. e. *abnormal conditions*—a task, in truth, of apparently unlimited range! Every disturbing influence, affecting any portion of the body whatever, is an abnormal condition; and it may at first sight appear as if we had undertaken to review at this point the whole subject of special pathology. Yet a moment's consideration will suffice to show that all disturbances, however diverse in character, can affect the circulation only by acting on the *blood* itself or on the *vascular mechanism.* If there be no alteration due to morbid processes in the condition or action of the heart, in the blood-vessels, or in the blood itself, the circulation must evidently remain unaffected, *i. e.* physiological. This, then, is our point of departure; aiming at a study of the circulation under pathological conditions, we shall confine ourselves to these two factors, the vascular system and the blood circulating therein. Thus, the problems requiring solution suggest themselves naturally; *How does the circulation behave when the vascular mechanism is deranged, how when the constitution of the blood is altered?* and the path to be pursued is naturally prescribed for us. It is not, however, possible properly to ss the beha [illegible] culation under pathological conditions except along the lines adopted in normal physiology. We have accordingly to consider in what manner the blood circulates in the different portions of the vascular system, under what pressure and with what velocity; as well as whether it thereby undergoes any qualitative or quantitative change, and if so, of what nature. It will be desirable, further, to consider in this connection the process of *transudation*, which depends so intimately and directly on the blood-stream, while the question of the influence of disturbances of the circulation on the function of individual organs will be appropriately discussed with the pathology of these organs. I crave permission, however, to neglect one portion of the subject, which should properly be considered here, and which regularly finds a place in the normal physiology of the circulation, *i. e.* the thorough discussion of those phenomena of the circulatory system which have developed into an integral part of the art of physical diagnosis. I have now in mind the doctrine of the heart's impulse, of the heart- and vessel-sounds and murmurs, and the doctrine of the pulse, all of them subjects to which you are introduced, better and much more profitably than would here be possible, in the lectures on the methods of physical diagnosis, and in the clinical teaching by the sick-bed. But do not, I beg of you, indulge in too high expectations. At present, pathology is far from being able to vie with her elder sister, the physiology of the circulation. The physiologist, for example, who finds a special pleasure in the study of the attractive details of the innervation of heart and vessels, will suffer bitter disappointment if he expects, in the exposition of the diseases of the circulatory system, to meet with a minuter analysis of precisely these relations, and of their influence. We are not, at present, in a position to do more than comprehend and demonstrate the, so to speak, gross disturbances of the circulation, disturbances which are, it is true, those of most serious import, and which consequently most closely concern the physician.

CHAPTER I.

THE HEART.

The heart as a suction-pump.—Abnormal tension in the pericardium an impediment to the filling of the heart.—Experiment.—Its explanation.—Action on the flow in the systemic arteries and veins, and on the pulmonary circulation.—Venous pulse.—Application to human pathology.—Retardation of the blood-stream.—Cyanosis.

The heart as a force-pump.—Conditions of regular cardiac action.—Occlusion of the coronary arteries.—Angina pectoris.—Sclerosis of the coronary arteries.—Nutritive disturbances, abscesses, and tumours of the cardiac musculature.

Work done by the heart in systole.—Its dependence on varying conditions.—Increased in consequence of valvular lesions.—Insufficiency.—Stenosis.—Synechia of the pericardium.—Experiments.—Artificial aortic insufficiency.—Artificial stenosis of the trunks of the pulmonary artery and aorta.—Application to human pathology.—Hypertrophy of the heart.—Its causes and effects.—Compensation of cardiac lesions.—Uncompensated abnormalities of the circulation.—Capillary pulse.—Overloading of the pulmonary circulation.

Idiopathic cardiac hypertrophy in labourers, gourmands, and of nervous origin.—Circulation in cor bovinum.

Rise of temperature and fatigue, sources of peril to the functional capacity of the heart.—Disturbance of compensation.—Effect on the circulation.—Dilatation of the heart's cavities.—Weakened heart.

Summary of the course of cardiac lesions.—Imperfections of the tricuspid.

Conditions of the frequency of the pulse.—Its variability in cardiac lesions.—Arythmia.—Influence of the pulse-rate on the pressure and velocity of the blood-stream.—Circulation in fever.—Influence of the pulse-rate on the circulation in cardiac disease.

In investigating the influence of disturbances of the vascular mechanism on the circulation, heart and vessels must, it is clear, be regarded separately, and the desirability of setting out with a problem as far as possible uncomplicated is no less apparent. We shall accordingly discuss, in the first place, *the behaviour of the circulation, when, the vessels remaining intact and the blood qualitatively and quantitatively unchanged, the heart presents deviations from its normal action.*

The normal action of the heart is well known to you. From the veins the blood reaches the auricles, passes during the ventricular diastole into the ventricles, to be then propelled by the contraction of the ventricular muscles at the systole into the arteries, on the left side into the aorta, on the right into the pulmonary; while at the same time the auriculo-ventricular and semilunar valves guard against its flow in a false direction. Accordingly, two phases have to be distinguished in the heart's action, the *filling* of the chambers with blood and the *emptying* of the same; in the former the heart acts as a *suction-pump,* in the latter as a *force-pump.* Now the nature of a circulation involves, it is true, an intimate connection and a mutual influence throughout both phases, but this does not exclude the possibility that, through some influence or other, the former or the latter may be the one primarily affected. On the contrary, an analysis of those disturbances of the circulation which depend on deranged action of the heart, cannot be satisfactory except it set out from the point where the morbid process has made itself primarily felt. We shall therefore commence with the first phase in the heart's action, and discuss the question *whether any morbid conditions exist by which the filling of the cavities of the heart with blood is impeded.*

Such an impediment is necessarily formed by *every* *effusion of fluid into the cavity of the pericardium, which is capable of causing a certain degree of tension of its wall.* For, normally, the pressure in the pericardium, as in the rest of the thorax, is not positive; on the contrary, the measurements of Jacobson and Adamkiewicz* on sheep and dogs prove it to be even negative, varying between − 3 and − 5 mm. hg. Now, in order that the tension in the pericardium may become positive and reach a certain elevation, it is necessary, on account of the ready distensibility of the sac, that the quantity of fluid be very considerable. In those cases especially where the fluid is very slowly effused, the power of accommodation shown by the pericardium is sometimes so extraordinary that several hundred cubic centimetres may be drawn off from it at the autopsy, although during life no signs of cardiac disturbance had been present. Inflammatory exudations will therefore, by their rapid increase in bulk, more readily bring about a considerable increase of tension than will simple transudations. But most dangerous in this respect are solutions of continuity of the heart and great vessels within the compass of the pericardium, in consequence of which the latter rapidly, often in a few seconds, becomes distended to an extreme degree with blood. How does the circulation behave in this situation?

On this subject experiment—which is attended with less difficulty than may appear at first sight—affords us the most reliable information. It is best to employ for the purpose a strong, middle-sized dog, which, as in all experiments on the circulation, and especially in those on blood-pressure, is curarized, respiration being carried on artificially. Access to the pericardium is most conveniently procured through a sufficiently large window in the left half of the thorax, formed by the resection of about three ribs. The sac is opened by means of the smallest possible incision, and a so-called clamp-cannula, such as is employed by physiologists for gastric fistulæ, is fastened in the aperture. This cannula may, according to F. Frank's method,† be connected with an air-reservoir, capable of being compressed at will, while the degree of compression is read off on a mercurial manometer attached to its side. It appears to me, however, that there will be less liability to error if, instead of filling the pericardium with air, we employ a liquid which will exclude all possibility of resorption during the short time occupied by the experiment, namely, oil. With this object, the clamp-cannula is connected by means of an india-rubber tube with a ⊢ piece, one limb of which communicates with an ordinary manometer, while the third serves for the injection or removal of the oil. If, further, a femoral or carotid artery—or, in case the pulmonary circulation is also to be observed, a branch of the *a. pulmonalis sinistra* in addition—be placed in connection with the kymograph, and an external jugular vein with the soda-manometer, the effect on the circulation of variations of tension in the pericardium can be read off with the greatest precision. If you now observe the kymograph, while the level of the oil-manometer remains at or below zero, you see in typical form the two curves characteristic of the arteries of the systemic and pulmonary circulation; on the one hand, the high pressure-curve of the femoral with its large respiratory elevations and depressions, and upon these the smaller and much more numerous systolic elevations; on the other hand, the very much lower curve of the *a. pulmonalis*, on which the respiratory and systolic elevations are represented as exactly synchronous with those of the femoral. The systolic elevations of the pulmonary nearly approach in height the corresponding tracings of the systemic artery, while the respiratory elevations, though less than those of the femoral, are still sufficiently marked, owing to the relatively strong insufflations which not only expand but also distinctly raise the entire lungs. Lastly, the level of the soda-manometer in connection with the jugular vein stands at about zero, with scarcely an indication of pulsation, but exhibiting regular depressions synchronous with the insufflations. Everything remains in precisely the same state —or at most the venous pressure ascends to slightly above zero—if you slowly inject into the pericardium a quantity of oil sufficient to raise the oil-level in the manometer to 30—40 mm. As soon, however, as you exceed this limit, and the oil-manometer indicates a tension of about 60—

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* Adamkiewicz and Jacobson, 'Med. Cntrlblatt.,' 1873, p. 483.

† F. Frank, 'Gaz. hebdomad.,' 1877, No. 29.

70 mm., or even higher, *you at once observe a fall of* 20—30 *mm. hg. in the femoral pressure, and, on the other hand, a rise of venous pressure to about* 60 *mm. soda.* These results become still more striking, when, by renewed injection, the oil-level has been raised to 100—120 mm. The femoral pressure now falls to about half its original value, and simultaneously the respiratory and systolic elevations, more especially the latter, become decidedly lowered. Similar characters are presented by the pulmonary curve, in which, it is true, the absolute depression is much less, the relative, on the contrary, scarcely less, than in the systemic artery. The pressure in the veins offers a most striking contrast to that of both arterial trunks, for it has now risen to about 100 mm. soda. While the oil-level remains constant, there is no change in the pressure or in the curves of the oft-mentioned vessels; and should, as usually happens after a little time, the tension of the pericardium become slightly relaxed owing to gradual stretching, the tube remaining closed, this is mostly accompanied by only a slight rise of the arterial, and fall of the venous, pressure. Not so, when the tube is opened, and the oil evacuated by the elastic recoil of the distended pericardium. The arterial curves now rise at a bound, the pulse tracings increase in size, and the venous pressure sinks, less rapidly it is true, but still with considerable celerity to its original level. If, however, instead of relieving the pericardium, you further increase the tension by renewed injection of oil, the phenomena above described become still more pronounced. The venous pressure rises higher and higher, the arterial curves approach more and more the abscissa, the systolic elevations constantly diminish *till at last they completely disappear.* This occurs first in the pulmonary, and usually as soon as the oil has risen to about 240 mm. A still higher tension is at other times needed; I have never, however, met with a case where the pulmonary continued to pulsate after the tension of the pericardium had risen to 320 mm. While the line described by the pulmonary is now straight, running parallel with, and quite near to, the abscissa, and only in some cases interrupted by slight insufflatory elevations, the curve of the femoral continues

for twenty to thirty seconds, and even longer, to present very small pulsations; whereupon these also cease, and it, like the pulmonary, comes to be represented by a line, which runs, as a rule, 10—15 mm. above, and parallel to, the abscissa. During this entire period, the level of the soda-manometer in the jugular steadily remains at 220, 240, and still higher. Clearly, the pulseless animal cannot be allowed to remain long in this condition; if, however, not more than one or two minutes or thereabouts have elapsed since the discontinuance of pulsation, it recovers almost without exception, on allowing the oil to escape from the pericardium. The pulse reappears first in the pulmonary, shortly afterwards in the femoral artery, and is depicted in the curve as a series of very large waves, following one another at long intervals, but gradually giving place to others of the original uniform size. The blood-pressure rises again rapidly and, as a rule, higher than at any time previously, remains for a brief period at this elevation, and then, if the tension in the pericardium continues minimal, sinks permanently to its original level. Meanwhile the venous pressure has again fallen to zero.

Now, how are these equally striking and constant experimental results to be explained? In order, as far as possible, to avoid misinterpretation, it will be best to fix our attention on one portion of the vascular system at a time. We shall commence by considering the systemic arteries, if for no other reason, because their curve presented the most striking alterations in our experiment. How is it, we ask, that *the arterial pressure falls as the tension of the pericardium increases, and that it rises as the latter diminishes?* We now know, it is true, that the high tension which normally prevails in the arterial system is dependent on a tonic contraction of the small arteries, whereby the channels conveying the blood to the capillaries are permanently maintained in a condition of relatively diminished calibre, a diminution only temporarily giving place in individual vessels to some degree of dilatation. We also know that the pressure can be regulated by increasing or diminishing this vascular constriction. But needless to say, the peripheral resistance is not the only factor involved in the production of the blood-pressure; were the peripheral resistance redoubled, were it capable of a quite unusual increase, the moment the heart failed to discharge a certain quantity of blood into the aorta, the tension in the arteries would be at an end. The quantity of blood thrown into the aorta by each contraction of the left ventricle must accurately correspond to that flowing off from the arteries into the capillaries during the period which elapses from the commencement of the systole to the end of the following diastole, *i. e.* during the intervals between two systoles. It is the maintenance of this proportion that is the source of *the constant mean tension of the arteries.* Suppose that, for some reason or other, the left ventricle commences after a given moment to eject a diminished quantity of blood, what will be the consequence? During the first systole the aorta will receive less blood than, owing to the high arterial pressure, flows off into and through the capillaries, *i. e.* the arterial system becomes *emptier;* the same thing happens at the second and third and each succeeding systole, while now the quantity of blood flowing off into the capillaries is, it is true, also gradually diminished; and this is repeated until the amount of blood discharged into the aorta at one systole and the amount passing into the capillaries during the interval between two systoles have again become equal. A constant mean tension, a constant mean pressure, is now re-established in the arteries; but it is *lower* than formerly in proportion to the lessening of the quantity of blood discharged at each ventricular contraction. Conversely, where the remaining conditions affecting the blood-pressure are unchanged, we may infer from a lowering of the mean arterial tension that the quantity of blood discharged at each systole has been diminished. That, however, the fall in pressure, which so promptly follows the increase of tension in the pericardium is actually dependent on this factor alone, is not merely to be inferred *per exclusionem;* on this point our curve affords us the most telling information. For *a lowering of the systolic elevations* accompanies *pari passu* the reduction of the mean arterial pressure, affording unmistakable evidence that, at each cardiac contraction, a smaller quantity of blood is thrown into the arterial system than before.

With a heart of normal functional capacity—and that its power remains unimpaired in our experiment is most strikingly proved by the behaviour of the arterial curves immediately after emptying the pericardium—a diminution in the quantity of blood ejected during systole can only depend on a diminution in the quantity present in the ventricle at the commencement of the cardiac contraction; in other words, on *a lessened flow of blood into the chambers during diastole.* But where does the blood remain which should, in regular fashion, have entered the heart, and why has it failed to enter? A glance at the manometer in the jugular reveals its hiding place; it has accumulated in the venous system, and the quantity present here is sufficient to give rise to really considerable tension, though this of course is not comparable to that in the arteries. Such overfilling of the venous system cannot possibly be the result of the great falling off in the fulness of the arteries, for nothing could be more preposterous than to assume that every decrease of tension in the arteries must be followed by an increased venous tension, the total amount of blood being as before; the arterial pressure in the dog sinks, after dividing the cervical cord, to 40—50 mm. hg., yet the venous pressure does not rise in the least. When, as in our experiment, the tension in the venous system increases to 100, 120, or even 200 mm. soda, this is to be attributed solely to a corresponding resistance, to an obstacle opposing the escape of blood from the veins into the heart, and *this obstacle is the abnormally distended pericardium.* The almost equal elevations of the oil- and soda-manometers at every period of our experiment is a numerical expression of the correctness of this reasoning; the venous pressure is augmented in proportion as the oil-level is raised by renewed injection of oil, and conversely. But since this is the case, because the venous tension increases with the increasing fulness of the pericardium, it is still possible for the circulation to be carried on; were it not so, the entrance of venous blood into the auricle, enclosed as it is in the pericardium, would be altogether out of the question. Yet, although the resistance offered by the pericardium is overcome by the venous pressure, the amount of blood reaching the heart from the veins in the unit of time is of necessity diminished, and that in proportion to the resistance, *i. e.* to the tension in the pericardium. Under these circumstances the venous flow suffers not merely a quantitative but a *qualitative* change; *the venous pulse becomes much more evident than is normally the case.* For although it is perfectly true that, even with a normal circulation, the veins which are situated in proximity to the heart display pulsations, synchronous with, and dependent on, the auricular systole,* these are usually so feeble as to require special methods for their demonstration; and since the auricle does not during its systole, still less during its diastole, offer any resistance worth mentioning to the instreaming blood, it is no essential departure from the truth to say that the venous stream, despite these pulsations, is uniform and continuous. The case is altered of course, when the flow of venous blood into the heart becomes impeded; for every aggravation or weakening of the impediment must make itself much more decidedly felt under such circumstances. If, now, the pericardium be so overfilled as to give rise to somewhat considerable tension, the venous blood may cease to enter at the moment when the abnormal resistance is augmented by the normal auricular contraction, and may enter only during the auricular diastole. The venous stream is then decidedly rhythmical, and not only may this character be observed with the greatest ease in the column of the soda-manometer, but there is also perceptible *a rhythmical turgescence* of the visible veins, most striking, of course, in proximity to the heart. This, it is true, does not, like the venous pulse in insufficiency of the tricuspid, originate in a positive wave produced by the contraction of the heart, but solely in a rhythmically recurring obstruction to the entrance of venous blood; yet it presents none the less the nature of a pulse. In this pulse the summit of the wave coincides with the auricular systole, while the depression corresponds with the auricular diastole, and is therefore, in greater part, synchronous with the ventricular systole. With respect to the latter, and in contrast to the systolic pulse of the carotid, the venous pulse is *presystolic.* The rhythmical character of the flow becomes more marked, the greater the tension of the pericardium, and thus everything progresses in an increasing ratio, till a moment finally arrives when the tension has become so great that the venous pressure at its acme can no longer overcome it. Henceforth, not a drop of blood enters the right heart from the veins; and the pulmonary artery, into which blood is no longer thrown, now marks on the paper of the kymograph a line parallel to the abscissa.

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* Cf. Gottwalt, 'Pflüg. Arch.,' xxv, p. 1; Riegel, 'Berl. klin. Wochenschr.,' 1881, No. 18.

But if the pulmonary artery supplies no more blood to the lungs, the pulmonary veins cannot deliver any, and the aorta is no better furnished with fresh blood than are the pulmonary arteries. The flow has now ceased in the systemic arteries, although some time will elapse before these, by their independent contractions, have propelled into the capillaries a quantity of blood sufficient to relieve their contents from all tension. The small, pulse-like oscillations, observable for a time in the carotid curve, are apparently nothing but slight movements communicated to the contents of the arteries by the contractions of the muscular left ventricle occurring simultaneously; as before stated, *a true circulation no longer exists.* But prior to this stage the pulmonary circulation has not altogether accorded with the systemic in its demeanour towards the abnormal tension in the pericardium. Even in their normal pressure-relations a great disparity exists. In the pulmonary circulation there is no such contrast as prevails in the systemic vessels between the height of arterial, and the lowness of venous, pressure. This is due to the absence of arterial tone in the vessels of the lungs, or at least to its insignificant character, and to the large diameter of the capillaries; indeed, the entire system of vessels constituting the pulmonary circulation resembles rather a simple system of branched elastic tubes. Were the pressure-relations in both the same, it would be impossible to see why, with an increase of pericardial tension, there should not occur in the pulmonary such a fall of arterial, and rise of venous, pressure as is observable in the systemic vessels. Yet what is possible in the systemic, is inconceivable in the pulmonary, circulation; for while in the former the arterial pressure, though reduced, always considerably exceeds the venous, even when this is very much augmented, so that the flow from arteries to veins does not cease; in the latter the pressure-values of arteries and veins rise and fall together. Hence it is that the strength of the inflowing stream is a measure of the tension in the pulmonary circulation; and since in our experiment, as shown by the pulmonary curve, the right heart sends an abnormally small quantity of blood into the arteries of the lungs at each systole, *the arterial pressure must fall, and with it*—despite the impediment to the entrance of venous blood into the heart—*the tension in the pulmonary veins.* Should any of you, however, find difficulty in conceiving how, under such circumstances, blood from the veins of the lungs can by any possibility reach the left auricle, I may remind you that normally the blood of these veins does not, like that of the systemic, enter the heart under a negative pressure, but has a positive tension little inferior to that of the blood in the pulmonary arteries, and that the energy of the venous flow is such as to overcome the resistance of a very material pericardial tension, even though a lowering of pressure to half or more has occurred.

This, then, is the inevitable effect which the filling of the pericardium with sufficient fluid to cause a high degree of tension exerts on the blood-stream in and through the heart, and thereby on the circulation in general. Immediately on the establishment in the pericardium of a positive tension of a few mm. hg., an obstacle is opposed to the entrance of blood from the systemic veins, which, on the one hand, increases the tension in the veins, and, on the other, diminishes the quantity of blood flowing into the heart in the interval between two successive systoles. Consequently, each systole forces less blood into the lungs, the pulmonary pulsations become smaller, and the blood-pressure in the pulmonary vessels, arterial as well as venous, sinks. This, however, involves of necessity a like diminution in the pulsations, and a corresponding reduction of the mean pressure, in the domain of the systemic arteries. These phenomena become more pronounced the more considerable the pericardial tension, till at last a moment arrives when not a drop of blood reaches the heart from the systemic veins, and the circulation ceases. Though the heart's chambers continue to contract, as shown by the pulsations of the oil-manometer, and more clearly still by means of glass tubes filled with a solution of common salt, previously introduced into either ventricle from the jugular or the aorta, and placed in connection with the manometers of the kymograph; yet these contractions are fruitless, and forward no blood to the corresponding arteries. Certainly, with affairs in this condition, the final cessation of the heart's action can only be a question of brief time. Not only the fact, however, that up to this point the circulation may be perfectly and rapidly restored to its original normal condition by disencumbering the pericardium, but also the continuance of the cardiac contractions after all movement of the blood has ceased, affords an unmistakable proof that it is not, as has been supposed, by interfering with the expansion of the chambers in diastole that the tension of the pericardium brings about the circulatory disturbances just described. An evident rise in the oil-level not uncommonly marks the very moment when the heart becomes paralysed and stops in diastole—most striking testimony that a pericardial tension of about 250 mm. oil is incapable of preventing the diastolic expansion of the cardiac cavities! Moreover, the expansion of the auricles would in any case be interfered with earlier than that of the ventricles.

In the light of these experiments, there can be no difficulty in understanding the disturbances of the circulation in human beings, in whom the pericardial tension is abnormally increased by any of the above-mentioned causes. Still we shall not depreciate clinical observation, if for no other reason, because it affords a valuable assurance that we have avoided in our experiments those sources of error to which our methods are liable. In fact, human pathology also teaches that the circulation is influenced, not by the absolute amount of the pericardial effusion, but solely *by the degree of tension produced by it.* In phthisis, a slow transudation into the pericardium, formed during the course of weeks or months, may acquire very considerable bulk; and yet, as already indicated, it produces not the least disturbance of the heart's action, simply because, owing to the gradual distension of the sac, there is not the least trace of tension in these cases; on manual examination of the closed pericardium *post mortem*, the finger comes into contact with a well filled but yielding bladder, and meets with no elastic resistance. Directly contrasting with this is the condition due to intra-pericardial ruptures of the heart or great vessels, where the effusion of a comparatively small quantity of blood, about 150—200 ccm., suffices to extinguish the circulation, and the individual perishes much more rapidly than the mere hæmorrhage would warrant. Of greatest interest, however, are the conditions attending inflammatory exudations into the pericardium. Here also the rate of development is certainly an important matter, so that small exudations of acute origin may be of more serious import for the circulation than the more bulky products of an insidious chronic process. In the commencement of acute pericarditis, where the layers of fibrinous exudation are still in contact, as manifested by the presence of a friction sound, the signs of disturbance of the general circulation are so slight, that the pulse of the patient, whose temperature is raised, is usually full, large, and hard, the skin hot, and the heart-sounds loud and strong. When, however, the friction-sound has disappeared, the area of cardiac dulness become greatly increased, and the cardiac impulse grown indistinct, —*i. e.* when a large quantity of fluid has been exuded into the pericardium—the arterial pulse is small and easily compressible, the heart-sounds, especially the second pulmonary, weak and muffled, while the visible veins in the face and neck and elsewhere, are more or less tensely filled, and stand out as thick cords, on which the rhythmical pulsations just described are most clearly observable. These signs are infallible evidence *that the blood-pressure in the aortic system and pulmonary circulation is lowered below the normal mean standard, and that in the systemic veins, on the other hand, it is abnormally elevated.* It follows directly from this that *the blood in the capillaries flows with diminished velocity.* For the difference of tension between arteries and veins has decreased, and, *ceteris paribus*, the rapidity of the stream from the one to the other is in direct ratio to this. While, however, the velocity of the stream is similarly altered in the systemic and pulmonary capillaries, it is otherwise with the *pressure* under which the capillary blood flows. For the uniform lowering of tension in the veins and arteries of the pulmonary circulation necessarily involves a similar change in the capillaries; in the systemic circulation, on the other hand, the inevitable consequence of the increased venous resistance, is an abnormal excess of blood-pressure in the capillary vessels; *the blood flows slowly, under an exalted pressure, through the capillaries of the systemic circulation.* The effects exerted by these profound alterations in the general circulation on transudation, and on the activity of the various organs will be thoroughly dealt with later on; only one point is here mentioned, because of its intimate connection with the circulation. In proportion to the tardiness of the flow through the capillaries, the blood will have a better opportunity of parting with oxygen and absorbing carbonic acid; the sluggish stream becomes markedly *venous.* This fact, and the overloading of the venous system, afford an explanation of the bluish-red, livid colouration assumed, under these circumstances, by all highly vascular organs—a change which, when it occurs on the surface of the body, is called *cyanosis.* Thus, to the symptoms occurring in pericardial exudation must be added cyanosis, seen either as a slight redness with a tinge of blue, and clearly apparent only in those portions of the body which are in general more highly coloured, like the lips, cheeks, ears; or observable as a very intense bluish hue of the skin of the face, lips, neck, and other parts of the surface.

While the abnormal tension of the pericardium lasts there is no change in the state of the circulation, and in some chronic cases of exudative pericarditis it may continue for many weeks. But the pericardial exudation may be attended by still greater dangers; it may even directly menace life, if the resulting pericardial tension is very considerable. For, although it cannot be denied that very many of the dangerous symptoms appearing in the course of this malady depend on complications which are more or less constantly associated with the pericardial lesion, such as pyrexia, the implication of the muscular structure of the heart itself; still the very surprising change in the picture of disease *which* *follows immediately on paracentesis of the pericardium,* proves beyond doubt that the abnormal tension of the latter contributes a large, if not the principal, share to the severity of the affection.

It need only be mentioned in conclusion that, besides overfilling of the pericardium with fluid, other pathological factors may occasionally oppose an abnormal resistance to the entrance of venous blood into the heart, and thereby to the regular filling of the latter. I have now in mind large tumours of the thoracic cavity, especially if situated in the neighbourhood of the heart itself; as, for example, extensive *aneurysms* and *mediastinal growths,* by means of which the organ is sometimes greatly displaced in a lateral direction, so as to pull on, and severely stretch, the large arterial trunks, or actually to bend the great veins at an angle with the heart. Pleuritic exudations, when very copious, can act in a similar manner. The circulation may in many other respects be directly or indirectly damaged by the presence of such tumours or exudations; but, in so far as they interfere with the filling of the heart with venous blood, they must be followed by the very same general circulatory disturbances as would accompany a corresponding increase of tension in the pericardium.

We now come to the second phase of the heart's action, that in which it acts as a *force-pump,* and performs its true task of setting the blood in motion. It is clear that whatever prejudices the regular evolution of this phase, whatever, consequently, exerts an injurious influence on the actual *work of the heart,* must be at least as important to the circulation as are those disturbances in the filling of the cardiac cavities which have till now occupied our attention. But the circumstance that no event of the sick-bed more frequently claims the earnest attention, and active interference, of the physician than these very derangements in the work of the heart, is especially calculated to excite our interest in this particular aspect of cardiac pathology. On calling to mind the intimate relations between the heart's activity and the condition and functions of all the organs of our body, you will readily understand how it is that disturbances in the heart's work are observed with extraordinary frequency in all varieties of disease. You have learned from physiology with what perfection—thanks chiefly to the action of the nervous system—the cardiac contractions can accommodate themselves in point of frequency, force, form, and efficiency to the most varied internal and external conditions of normal life, so that the ventricles shall act at each systole to the greatest advantage of the organism; and you will soon hear that the capacity of these regulative mechanisms far more than meets the demands of ordinary, or physiological, life. Yet, however exquisitely the regulative contrivances in the heart may act, not merely do conditions exist where they prove inefficient, but circumstances, too, in which, as you will learn, new and abnormal conditions that are by no means indifferent for the circulation, spring out of this very regulative activity. The analysis of the circulatory disturbances appearing under such circumstances constitutes one of the most important, and therefore interesting, tasks of this part of morbid physiology.

The contractions of the heart, you are aware, are physiologically initiated and controlled by the *system of ganglia* embedded in its musculature. It is not known whether independent morbid changes occur in the cardiac ganglion-cells, and the data adduced in evidence are, so far, much too meagre to justify us in drawing any conclusions whatever.* We know, indeed, that the excitability of the ganglia is dependent on *the presence of oxygenated blood*, which is conveyed to them by the coronary arteries. In what manner the cardiac activity reacts to changes in the chemical constitution of the blood—I remind you of the cardiac poisons—or to alterations of its temperature, we shall have to inquire in another place. Here, where the composition of the blood is assumed to be normal, we are interested merely in whatever effects may be exerted on the cardiac ganglia by *derangements of the circulation through the coronary vessels.* That the cessation of the coronary circulation destroys the excitability of the ganglia, may be inferred *a priori* from our experience of the life of the nervous centres gained in other directions; moreover we are fortunately in a position to offer direct proof of the fact. A considerable time has elapsed since v. Bezold[*] proved that, on compressing the *a. coron. magna s. sinistra* in the rabbit, the heart of the animal quickly ceases to beat. He observed that both right and left hearts sometimes stopped simultaneously, but that more frequently the stoppage of the right followed later. Samuelson,[†] who recently repeated Bezold's experiments, mostly witnessed, on cutting off the coronary circulation, a gradual weakening of the cardiac contractions, ending in their complete extinction, first on the left, and afterwards on the right, side. But when performed on the dog, the experiment has a still more remarkable course ;[‡] for in this animal, the ligature of any large branch of the *a. coron. sin.* or *dextra* has at first no effect whatever on the rhythm or vigour of the cardiac contractions, nor consequently on the blood-pressure ; but after the lapse of ninety seconds, on an average, the heart-beats begin to be somewhat irregular and infrequent, yet still without affecting the blood-pressure, till *suddenly and at the same instant both chambers stop in diastole.* From this standstill, which occurs, on an average, not later than two minutes after occlusion of the branch-artery, there are no means of arousing the ventricles to new life and renewed contraction ; it seems as if a deadly poison had for ever destroyed the heart's excitability. Accordingly, it is, in all probability, the system of ganglia which is affected in this direct fashion, although the anatomical distribution of the ganglion-cells within the muscular mass makes it impossible to distinguish with certainty whether the action of the arterial ischæmia is exerted on the nervous or muscular elements. Yet I am unable to conceive how, with a marked independence of the muscles of the left and right ventricles, the one from the other (of which I shall produce numerous proofs further on), a limited arterial ischæmia could, in such deadly manner, paralyse irrestorably the whole cardiac musculature. For I repeat, the closure of one or both coronary trunks is not necessary ;

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* Cf. Putjatin, 'Virch. Arch.,' lxxiv, p. 461.

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[*] v. Bezold, 'Med. Ctrbl.,' 1867, p. 352 ; 'Untersuchungen aus dem physiol. Laboratorium zu Würzburg,' 1867, p. 256.

[†] Samuelson, 'Ztschr. f. klin. Med.,' ii, p. 12.

[‡] Cohnheim and v. Schulthess-Rechberg, 'Virch. Arch.,' lxxxv, Hft. 3.

any one branch of a certain size, no matter which, is sufficient, though the occlusion of very small branches is without any recognisable influence on the function of the heart. It would here lead me too far, were I to dwell at length on this remarkable experiment, and especially were I to attempt to explain why it is that the closure of the coronary arteries in the rabbit has not always the same effect as in the dog; on the other hand, it will be interesting to you to learn that the experiment has a really practical bearing on human pathology. Not merely that cases of sudden death are on record, where the autopsy revealed as sole—and, as we now know, sufficient—cause of death, embolic obstruction of one of the larger branches of the coronary arteries; we are also undoubtedly justified in utilising our experiment to explain those much commoner, but no less suddenly fatal, cases where extreme *sclerosis of the coronary arteries,* but no embolism, not even thrombosis, can be demonstrated *post mortem.* The explanation to be adopted here is the same as is resorted to in those by no means rare examples of softening of the brain which set in with the clinical picture of apoplexy, although nothing is found after death save a chronic sclerosis of the arteries supplying the area of softening. In both cases the lumen of the artery becomes narrower and narrower, owing to the gradually advancing disease of its wall, till a point is reached where the quantity of blood indispensable to nutrition—in other words, to the maintenance of function—can no longer pass through the vessel, and now there takes place, in the one case, the interruption of nerve-conduction, in the other, the fatal action on the cardiac ganglia.

But if you accept this interpretation, you will very properly ask—What was the character of the heart's action at the time when the coronary arteries, though still pervious, *no longer permitted the passage of a normal blood-stream?* Certainly, a justifiable question, and yet I am not in a position to give you a satisfactory answer. For, though it is established beyond doubt that if a somewhat extensive segment only of the heart be completely deprived of arterial blood, death rapidly ensues, we know little that is certain of the influence possibly exerted on the action and excitability of the ganglia by that impairment of the circulation through the vessels of the heart which is inseparable from sclerosis of the coronary arteries. Pathologists have for a long time been disposed to connect the peculiar neurosis, known under the name of *angina pectoris* or *stenocardia*, with sclerosis of the coronaries. *Angina pectoris* is characterised by paroxysms of violent pain, radiating in various directions from the præcordial region, at the same time associated with a feeling of indescribable anxiety and dread of impending dissolution, and frequently accompanied by intense dyspnœa. During the attacks, the pulse is usually irregular, and as a rule, small and empty, or even intermittent; sometimes, however, it is very full, hard, and extremely frequent. The duration of the paroxysms varies from a few minutes to several hours. Now it is quite true, that in individuals who have suffered during life from *angina pectoris*, or perhaps succumbed to an attack, there has repeatedly been found *post mortem* a more or less extensive and advanced rigidity and sclerosis of the coronary arteries. Nevertheless, a true causal relationship need not therefore exist, especially as it often happens that no trace of disease is to be found in the coronary arteries of such subjects, and—what is still more common—that a very high degree even of coronary sclerosis is met with in persons who have never had an attack of angina. Even if the statistics telling in favour of a connection between both processes were more satisfactory than is really the case, this would be little to the purpose. It would always be open to suppose that the circulation through the coronaries, being already impeded, had been still further impaired by some transient accidental circumstance or other; such a supposition, however, is incapable of proof. But, turning from the consideration of these paroxysms, let us look at the evidence at our disposal with regard to what is, to my mind, a much more interesting question, namely, whether the action of the cardiac ganglia, either during the interval between two attacks, or in their entire absence, presents any kind of permanent deviation from the normal, which might possibly be attributed to an insufficient supply of arterial blood? On this point experience, as already stated, affords little of a positive character. On the one hand, chronic end-

and mes-arteritis of the coronaries is, especially in advanced life, so extraordinarily frequent, and on the other, anatomical examination of arteries *post mortem* is so far from being a fair criterion of the extent to which they were *intra vitam* permeable, that the utmost caution must be observed in coming to a conclusion. So much is at any rate certain, that in many cases where, judging from the anatomical appearances presented by the coronary arteries, we are obliged to admit that the impediment to the circulation in them must have been very considerable, no symptoms of any kind of disturbance of the heart's action had been present during life; and the case is not necessarily altered by the presence of single, or even of numerous, so-called *myocarditic fibrous indurations*, the witnesses in the heart itself to the poverty of a blood-supply, in many places insufficient even to maintain the vitality of its muscular fibre.

For the fact that severe *disturbances of the nutrition of the muscular tissue of the heart*, very commonly form a sequel to the affection of the coronaries, introduces a new element of difficulty, and complicates not a little the whole question. It is now known that the very great majority of the myocarditic indurations just mentioned, whether they represent the final stage of typical necrotic foci, so-called *cardiac infarcts*, or constitute the residual product of a slow and imperceptible destruction of some of the muscular fibres, are due to an advanced sclerosis of the small branches of the coronary arteries supplying the affected part. For this reason, they are most frequently met with in those portions of the heart where the arterio-sclerosis is usually most intense, namely, in the areas supplied by the descending branch of the left coronary artery. Furthermore, most pathologists are probably now unanimous in regarding numerous cases of fatty degeneration as the sequelæ simply of severe coronary sclerosis. These, it is true, constitute but part of the fatty hearts which come under observation, for *fatty metamorphosis*, or *fatty degeneration*, is certainly the most frequent of all the nutritive disturbances occurring in this organ. We shall have to go into its various causes later on; here it is sufficient to point out that it may be acute or chronic in origin, may attack either the right or the left ventricle alone or both together, and that, as in all morbid processes, there are very different degrees of it. The degeneration usually affects first the papillary muscles, next the subendocardial layer of muscular fibres, and finally, in extreme cases, the whole thickness of the muscular wall. But while many of the fatty degenerations of the heart have nothing to do with disturbances of the coronary circulation, this is more universally true of some other pathological processes and conditions, by which the anatomical and histological integrity of smaller or larger sections of the heart's musculature is damaged. Among these are *amyloid degeneration* of the myocardium; further true inflammatory processes of the heart-muscle, both the rarer more diffuse forms, and the more common *cardiac abscesses*, such as are observed in glanders and in pyæmia, and occasionally also, as the result of embolism, in ulcerative endocarditis; and lastly, all *tumours* situated in the muscular wall, as carcinomas and sarcomas, the larger caseous tubercles and gummata; the *entozoa*, as cysticerci and echinococci.

You see there is no scarcity of pathological processes by which the heart-muscle is more or less damaged in structure or in chemical composition. Some of these involve only limited portions of the muscular tissue; others, on the contrary, are more diffuse; and they present, in other respects, the utmost variety of character. They have, however, one feature in common, in that *they all cause a loss of contractile substance*, of that substance, that is to say, which executes the work of the heart. The result, consequently, of all these processes will be *a deterioration*, more or less, *of the heart's working capacity*. But since the myocardium, like every other muscle, cannot work without an abundant supply of arterial blood, it may safely be assumed that a degree of coronary sclerosis capable of opposing a considerable obstacle to the stream of arterial blood into, and through, these vessels, will also depress the functional power of the cardiac musculature. While we are thus enabled to discuss the group of circumscribed or of diffuse affections of the heart-muscle and sclerosis of the coronary arteries from the same point of view, no long period has elapsed since the following line of reasoning was in vogue. A heart whose working power has deteriorated must either throw into the arteries by its contractions a given quantity of blood with diminished force, or only (which amounts to the same thing) discharge a smaller quantity. The consequence must be that an abnormally small amount of blood will reach the arteries at each systole, and that therefore, not only will the single pulsations become smaller, but also—for reasons previously laid down—the mean arterial pressure fall. This sounds plausible enough, but only a moment ago I dwelt on the fact that very severe coronary sclerosis is very frequently found at the autopsy of individuals, in whom, during life, no sign had pointed to derangement of the circulation; and there exists a multitude of analogous experiences with regard to the diseases of the myocardium. Thus, circumscribed tumours of the heart-muscle do not usually betray their presence by any morbid symptom whatever, even though a large number of nodules be scattered throughout both ventricles. Myocarditic indurations, also, even when so numerous in a region as to lead to the protrusion outwards of the affected part in the form of a partial cardiac aneurysm, often remain quite latent till death. Moreover, everyone with a large material for observation at command, has seen cases where the autopsy reveals severe alterations in the heart-muscle, *e. g.* such a host of connective-tissue indurations and necrotic infarcts that one meets them at every incision into the muscular wall; and yet the pulse had betrayed, *intra vitam*, no deviation from the normal, in particular no lowness of tension. But still more; it may be shown experimentally, and that too in animals whose hearts are not distinguished by special vigour or power of resistance, that the loss of very extensive portions even of the contractile substance is not necessarily disadvantageous to the blood-pressure and character of the pulse. In a rabbit, access to whose heart is procured by opening the thorax and pericardium, whole portions of the right or left ventricle can be compressed and thrown out of action by means of broad clamps furnished with strong springs; and *yet the arterial curve does not display the slightest change.* A considerable section of the heart-muscle is here completely isolated—and yet no influence whatever on the arterial pressure! [illegible] should anyone attach special importance to the fact that, in all these cases, only smaller or larger, and at any rate circumscribed, portions of the contractile substance are rendered inactive, while the remainder continues quite unchanged, I may allude to fatty heart, and to that variety where, as a rule, the whole of the muscular fibres of right and left ventricles are attacked with equal severity, namely, the fatty heart in severe forms of anæmia, in the so-called *pernicious anæmia*, for example. For, in quite a number of typical and fatal cases of this disease, the pulse, which is strong, mostly somewhat frequent, but in other respects quite regular, and the good arterial tension, most vividly contrast, up to a very short time before the fatal termination, with the waxy pallor, loud systolic cardiac murmurs, and painful muscular feebleness of the patients. How is it to be explained that pulse and blood-pressure have retained their normal characters, despite such profound alterations of the entire myocardium ?

In the syllogism above given one of the premises must clearly be false, and indeed the error may be readily detected. That coronary sclerosis and the various affections of the heart-muscle must permanently diminish the energy of the heart, even the most determined sceptic will not dispute ; but is it true that less blood is now ejected into the arteries at each systole than formerly, when the functional capacity of the myocardium was still unimpaired ? This conclusion would be perfectly legitimate, were the quantity of blood expelled by the normal heart at each contraction constant, and directly proportional to the muscular power of the ventricle. But in reality this is out of the question. *The work done by the ventricle at each systole, i. e.* the product of the amount of blood set in motion and the height of pressure, *is a quantity varying, under normal conditions, within very wide limits.* Let us confine ourselves, for sake of simplicity, to the left ventricle—the same considerations, *mutatis mutandis*, evidently hold good for the right—and we find that the height of pressure, *i. e.* the arterial tension, being constant, a change in the frequency of the pulse is sufficient to [illegible] or to diminish the systolic work. Observe [illegible] posing the heart of a living rabbit, and applying to one of its vagi the electrodes of an induction apparatus. The moment a current of moderate strength passes through the nerve, you see, as the pulse becomes slower, an increased diastolic expansion of the ventricle; and since the chamber is emptied at the next systole to the same extent as before, this is nothing short of an increase in the amount of work done. Similarly, the quantity of blood entering the ventricle during diastole must vary proportionally to the velocity of the venous blood-stream. In mountain climbing, for example, or other strenuous physical exertion, the circulation through the muscles is very abundant and rapid; consequently a larger amount of blood reaches the heart through the great veins in the unit of time, and each systole must now eject a larger amount, or in other words, perform more work. A contrary condition prevails in a state of complete bodily rest; this is certainly the case during sleep. We have here presupposed that the resistance to be overcome by the ventricular contraction is always the same, but this is true only conditionally, and within certain limits. As compared with our knowledge of the diurnal variations in the frequency of the pulse and in the temperature of the body, we possess, owing to the imperfection of the means at command for its determination, little accurate information with regard to the daily behaviour of the blood-pressure. Still, leaving out of account the respiratory variations, we are at least aware that, under quite normal circumstances, for example, during physical exertion or digestion, the arterial pressure, and with it the work of the ventricle in systole, rises higher than at other periods. The heart occupies no exceptional position amongst the mechanisms of the animal body; the machine works thus surely and perfectly, *because it is so adjusted that it can promptly accommodate itself to the varying internal and external conditions.* We can no more speak of a "normal" amount of work, as a definite absolute value, in the case of the heart than in the case of the stomach or kidneys; for the "normal" varies with the varying state and behaviour of the rest of the body. The criterion of health consists rather in the ability of the heart to comply at once with the varying demands on its work. But if the organization of the human heart be such that it is capable of meeting very excessive demands, it need excite no surprise, should a lessening of its energy leave it still capable of fulfilling the ordinary average tasks required of it. To what extent the normal heart can do justice to these demands, pathology alone fully informs us.

The work done by the heart—to this we adhere as the starting point of our entire discussion—is determined by the quantity of blood reaching the ventricle during diastole, and the amount of resistance to be overcome by the heart in propelling it into the arteries; and because both factors are normally liable to constant variations, the amount of work done by each contraction is also probably a constantly varying quantity. Nor can there be any morbid factors capable of affecting the work of the heart-muscle, except such as act on the arterial resistance or on the diastolic blood-quantum. Should it be asked, however, what are the pathological processes calculated to augment the work of the heart by increasing one or the other factor, or both together, we must evidently include here the frequent recurrence, or extreme augmentation, of physiological processes. But the pathological character of these augmentations is still more apparent when they are brought about by circumstances having no analogy in physiological life, in other words, when the conditions increasing either the diastolic blood-quantum or the resistance opposed to the emptying of the ventricles are altogether abnormal.

Of such abnormal conditions, none are commoner or more important than *imperfections in the valves of the heart-pump*, or, as they are commonly called, *valvular lesions*. The office of the valves is, you are aware, to secure that the blood set in motion by the heart shall take and maintain that direction which alone subserves the circulation. The auriculo-ventricular valves accomplish this by swinging up in the ventricle during systole till their lines of contact meet, while the *chordæ tendineæ* arising from the papillary muscles guard against their inversion into the auricles. The semilunar valves attain the same object by flapping down towards the ventricle in diastole till their lines of contact come into apposition. Bearing in mind this mechanism, it at once becomes evident under what circumstances the valves will be unable to effect the closure of the corresponding ostia, or in other words, *insufficient*. This will occur, in all cases, where the flaps are too short to allow their lines of contact to meet, or where defects exist in their substance. In the auriculo-ventricular valves it will also take place when the *chordæ tendineæ* are abnormal, whether it be that, through shortening, the cusps are held fast against the papillary muscles and thus prevented from closing, or that their laceration permits the segments to overstep the mark and become inverted into the auricle. These lesions are mostly the product of an *endocarditis valvularis*, which has terminated, in part, in contraction, and, in part, in ulceration, loss of substance, and perforation of the valves; the last not uncommonly after the disease had previously gone on to the formation of small valvular aneurysms. It cannot be disputed, however, that in a minority of cases the valvular incompetency has arisen without the pre-occurrence of endocarditis valvularis. I refer to so-called *relative insufficiency*, where the perfectly normal valves, after having for a long period satisfactorily fulfilled their function, become, in consequence of the subsequent occurrence of an abnormal dilatation of the corresponding cardiac cavity or vascular lumen, too short to cover the over-capacious ostia. Such relative insufficiency, or, perhaps still better, *incontinency*, is most commonly met with in the tricuspid. It also sometimes occurs in the valves of the left heart; but it is rather true endocarditis that is in both—in the aortic valves certainly oftener than in the mitral—the cause of the valvular imperfection. So far as the effect on the blood-stream is concerned, it can naturally occasion no difference whether the insufficiency has been brought about in one way or the other. But what is this effect?

Speaking generally, a portion of the blood must, in every case of valvular incontinency, be diverted from its natural direction, and the normal stream be thereby impoverished. But a special consideration of each of the valves in question is indispensable, if we desire to understand the precise influence of these lesions on the circulation through the heart. The least complicated conditions are presented by insufficiency of the semilunar valves. For here the result of the incontinency is *the regurgitation*, during the ventricular diastole, *of a portion of the blood from the aorta or pulmonary artery, as the case may be, into the corresponding chamber;* and the latter is consequently fed during diastole with blood from two sources, normally from the auricular, and abnormally from the arterial. Matters are somewhat more complicated in insufficiency of the auriculo-ventricular valves. Let us take the mitral first. Here, part of the blood, which has entered the left ventricle during diastole, will be thrown back at the next systole through the incontinent valve, at least as far as the left auricle; whether also into the lungs, and if so, how far, depends on the degree of insufficiency, the muscular power of the ventricle, &c. Do not forget, however, that the retrograde movement is of very brief duration, and coincides only with that part of the systole, during which the rapid ascent of pressure in the ventricle, that is to say, its active contraction, takes place; in the interval following, during which the ventricle remains firmly contracted, the blood again flows out of the pulmonary veins into the relaxed auricle, so that this is filled with blood from two sources, in a normal manner from the lungs, and in a perverted one from the left ventricle. Yet this is not all. For, in the first place, the left ventricle will also henceforward receive during its diastole an abnormally abundant supply of blood, since now, not merely the normal, but in addition the regurgitated, blood flows in from the auricle, or rather, as you will soon hear, is driven in by its more forcible contraction. Again, in the second place, the over-filling of the left auricle, or the direct regurgitation of the blood into the lungs, as the case may be, involves an impediment to the circulation through these organs, in other words, *the resistance in the pulmonary system is increased,*—an item of essential importance in the work to be done by that portion of the heart whose duty it is to overcome this resistance, namely, the right ventricle. It is apparent that, with the exception of the circumstances last mentioned, these observations also hold good for insufficiency of the tricuspid.

But it is indispensable to the regular action of the heart,

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that the flaps shall so act that the ostia, which are closed at the right moment, shall be at other times open. The auriculo-ventricular valves are opened, as you know, at the commencement of the diastole of the ventricles, the arterial at the commencement of their systole. Now there are a number of morbid processes, by which the opening of the ostia is, in a greater or less degree, impeded. The most important part is played here by *the inter-adhesion of two valvular segments;* an event which of necessity leads to encroachment on the area of the affected orifice, should the evil remain unremedied by a corresponding elongation of the new valve formed by adhesion. A stenosis will still more certainly result, when the mobility of the adherent valves is lessened by *the deposit of lime-salts,* and their closure by the pressure of the instreaming blood becomes, in consequence, difficult or even impossible. In fact, we have not infrequently an opportunity of convincing ourselves how considerable are the deposits of a thrombotic character, which may be seated on a valve, semilunar or cuspid, despite the absence during life of all signs of stenosis. As long as the deposits are soft, they constitute no obstacle, worth mentioning, to the circulation; a circumstance which sometimes tells in a surprising way, especially in so-called *endocarditis ulcerosa.* So soon, however, as a somewhat considerable portion of the valves has undergone calcification, an impediment to the circulation is the result. During extra-uterine life, this condition is observed in the vast majority of cases in connection with the left auriculo-ventricular orifice, which is often transformed into a narrow, button-hole-like slit. Next in point of frequency comes the aortic orifice, which may in extreme cases be so narrowed that a tolerably thick sound can only with difficulty be insinuated through it. It is much more rarely seen in the pulmonary orifice, which, on the other hand, often becomes the seat of stenosis in consequence of faulty development in fœtal life. Lastly, isolated stenoses of the right auriculo-ventricular orifice are to be classed among the greatest rarities.

We have next to deal with those narrowings of the cardiac ostia, or of the conus arteriosus, which are due to compression from without or to tumours in the heart itself, and which, by reason of their less frequent occurrence, are of inferior importance to the adhesions and calcifications of the valvular segments. Thus, the pulmonary ostium may be greatly narrowed by the pressure of an aneurysm of the aorta descendens. Again, an echinococcus or a large cancer-nodule in the left ventricle may lead to severe obstruction of the aortic or mitral orifice. Cicatrices may also occasionally be observed in the heart stretching like an actual diaphragm across a great part of the conus arteriosus of the right or left ventricle.*

The influence exerted on the circulation through the heart by all these varieties of stenosis, whatever their origin, may be stated very simply; it consists in *the establishment through their agency of an abnormal resistance*, by which the resistance already opposed to the emptying of the corresponding cavities of the heart is augmented. If the stenosis is situated at the outlet of the ventricle, *i. e.* in the ostium arteriosum or in the conus arteriosus, it is the ventricle that is affected by the increased resistance; if, on the other hand, one of the auriculo-ventricular orifices is narrowed, the auricles meet with a greater or less degree of resistance during their systole, while normally the amount to be overcome by their contraction is practically *nil*. In stenosis of the mitral, however, the effects of the abnormal resistance will extend as far back as the right ventricle, for the auricular contraction only takes place during the last third of the ventricular diastole, and previously to this it is principally the tension communicated to the pulmonary circulation by the right ventricle that drives the blood forward. While, therefore, insufficiency influences the work of the heart chiefly by increasing the diastolic blood-quantum, stenosis acts by enhancing the resistance opposed to the evacuation of the cardiac cavities. In very many valvular lesions, it is true, especially in those leading to contraction of the orifices, both conditions unite in increasing the demands on the work of the heart, for only too often insufficiency goes hand in hand with stenosis.

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* Cf. Graeffner, 'Arch. f. klin. Med.,' xx, p. 611; Landmann, ibid., xxv, p. 510; Leyden, 'Virch. Arch.,' xxix, p. 197.

It will be advisable to consider in connection with stenosis another pathological condition which, though essentially dissimilar in nature, has one point in common with it, that it augments the resistance opposing the heart's contraction—I mean the complete adhesion of the two layers of the pericardium, so-called *synechia*, which so commonly remains after a severe fibrinous pericarditis. To be sure, synechia of the pericardium would scarcely, as such, offer any very great resistance to the contraction of the heart-muscle, since normally the parietal layer is always in immediate contact with the visceral; and, in fact, the entire obliteration of the sac is often enough a *post-mortem* discovery, for which no symptoms *intra vitam* had prepared us. But, associated with the pericarditis interna, it is by no means uncommon to find a so-called *pericarditis externa*, that is, an inflammation of the pleura pericardiaca and of the mediastinal connective tissue. It thus comes to pass, that the synechia of the pericardium is frequently combined with firm adhesions between the parietal layer and the anterior wall of the thorax, the mediastinal layers of the pleura, the diaphragm, and even the structures of the posterior mediastinum. But where such attachments exist, the heart must by its contractions overcome the opposition of all these structures, and the resistance opposed to its work is consequently increased to a considerable degree above the normal.

Now, should one of the morbid conditions just described be established in connection with the heart, it follows as a direct conclusion from our recent discussions that the work done by the organ must be augmented to correspond with the increased demands upon it; and this will occur whether the entire heart or only single parts be concerned. At any rate this is the result to which we have been led by our reflections. But in order to determine whether this increase really takes place, we shall again have recourse to the experimental method. If one of the lesions described above be produced artificially in a healthy animal, a simultaneous examination of the arterial and venous circulation, on the one hand, and of the intracardiac pressure, on the other, must afford reliable information on the point at issue. With this object a very simple, but it is true imperfect, method of demonstration may be resorted to. Nothing more is necessary than the production of artificial aortic insufficiency by perforating the aortic valves of an animal.[*] The experiment may almost always be successfully carried out on the rabbit, and with still greater certainty on the dog. A thin metallic sound, furnished at its foremost extremity with a button, is introduced into the carotid in the direction of the heart, and if carefully manipulated, may quite easily be made to perforate at least one, sometimes two, or perhaps all three segments; or one may even succeed in partially tearing them from their attachment to the aorta. That laceration of the valves has been successfully effected is not merely apparent to the operator as he guides the instrument; as a rule, a loud, mostly whistling murmur, audible over the base of the heart, at once affords proof of positive success. Most unmistakable information is, however, derived from the arterial pressure-curve, where the peculiar characters of the pulse of aortic insufficiency, shortly to be discussed, immediately make their appearance. But although there is no doubt that the aortic valves are perforated, and no longer able to effect complete closure of the orifice during the ventricular diastole, *the mean arterial pressure continues at precisely its former level*, nor is the venous pressure in the least influenced by the operation. This result, while making it extremely probable, that the work done by the left ventricle has increased in consequence of the insufficiency, does not, however, directly prove it. There is, moroever, in the experiment the inherent drawback, that the amount of insufficiency is not under control, since the number of segments perforated and the size of the perforations are more or less matters of chance, and there is no possibility of determining the extent of the injury *intra vitam*. Much more instructive therefore, although more complicated, is another experimental procedure, by which *stenosis*, and not insufficiency, *of the arterial ostia* is artificially produced.

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[*] This experiment was first communicated in the first edition of these lectures, vol. i, p. 38; described more in detail, as well as supplemented and developed, especially in the clinical direction, by Rosenbach in his inaugural thesis, 'Ueber artificielle Herzfehler,' Breslau, 1878, and 'Arch. f. experiment. Path.,' ix, p. 1; since wrongfully called in question by J. Goddard, 'Kunstmatig opgewekte gebreken van het ostium aortae,' J. D. Leiden,

This experiment, like that on positive pericardial tension, is carried out on a curarized dog, whose respiration is maintained artificially; the first step in it being the formation of a large window in the left half of the thorax by an ample resection of the ribs. The pericardium is then opened at its upper end, in the neighbourhood of its reflection, and the cellular and adipose tissues binding together the aorta and pulmonary artery immediately above their origins are divided by means of two pairs of forceps. The greatest caution must be exercised here, since the thin-walled pulmonary is extremely susceptible of injury. A strong thread is then passed round the artery, of which it is desired to produce stenosis, and the ligature is secured in a loop-knot, such as is employed in surgery under the name of "Graefean." The lumen of the aorta or of the pulmonary artery can now be more or less constricted at discretion by means of the ligature. The curve of the *arteria femoralis* (this vessel being connected with the kymograph) and a soda-manometer in connection with the *vena jugul. sin.* simultaneously supply us with information as to the pressure relations in the systemic vessels. The intracardiac pressure is registered by one of the manometers of the kymograph, connected with a comparatively wide glass tube introduced into the corresponding ventricle. The glass tubes employed for this purpose are closed at the cardiac end and provided with a lateral aperture; they should be filled with a 0·6 per cent. solution of common salt and introduced into the heart; the introduction being carried out, on the right side, from the *v. jugul. ext. dextra*, and on the left, from left auricular appendix, which is then secured by a ligature round the tube. The tube may be most conveniently connected with the manometer of the kymograph, after the method of Goltz and Gaule,* by means of another forked one, the two limbs of which serve as manometers. One limb is provided with a valve allowing the ascent, but not the descent, of the column of mercury, and acts as a maximum-manometer, while the other forms a manometer of the ordinary kind.

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* Goltz and Gaule, 'Pflüg. Arch.,' xvii, p. 100.

The animal being thus prepared, let us begin with the production of *stenosis of the pulmonary artery*, regulating its severity by the amount of twist communicated to the ligature-rod. Now, you may increase the twist either slowly and gradually but continuously, or intermittently, and carry it to such a pitch that a very marked constriction of the pulmonary artery becomes apparent not only to the examining finger, but to the naked eye—for all that, *you cannot detect the slightest change in the femoral curve or in the manometer in the jugular;* mean pressure, pulse, and respiratory undulations, everything remains exactly as before. A change occurs only when the stenosis is carried beyond a certain point. *The arterial pressure then undergoes a steep and sudden descent,* while at the same time the level of the venous manometer rapidly rises; the femoral curve approaches to within 10—15 mm. of the abscissa, the respiratory undulations cease, the pulsations become extremely small, their rhythm considerably retarded and quite irregular; and, if the ligature be not loosened, life is in extreme danger. As soon, however, as the ligature is untwisted and the passage through the pulmonary artery thus opened up, the arterial pressure-curve reascends (its pulsations succeeding each other at first slowly, but by degrees more rapidly) till it, as a rule, reaches, and for a short time maintains, a level higher even than the original, while at the same time the level of the soda-manometer falls almost to the zero point.

You see, the last part, the conclusion of this experiment harmonizes perfectly with the pericardial one, while the first part presents a complete contrast. For, while in the pericardial experiment, the lowering of arterial, and the elevation of venous, pressure were from the commencement exactly proportional to the increase of tension in the sac, stenosis of the pulmonary has, for a long time, no influence whatever on the circulation through the systemic vessels. An examination of the intracardiac curve affords an explanation of this striking difference. The moment the pulmonary ligature is tightened even slightly, *you observe an immediate rise of intracardiac pressure on the right side;* and the more the stenosis is increased, the higher is the ascent of the pressure-curve of the right heart. This is expressed most elegantly by the curve obtained from the maximum-manometer; every turn of the rod, even the gentlest, is here at once responded to by a step upwards. The manometer of ordinary construction also represents this appearance quite clearly. Indeed, it reveals another interesting phenomenon not observable in the maximum curve, namely, an extension of the systolic excursions of the mercurial column, keeping pace with the gradually increasing constriction. True, in the case of the right heart this extension is not very striking; yet, where the narrowing was extreme, I have sometimes seen the distance between the systolic summit and the diastolic depression almost doubled. The rise of intracardiac mean pressure, if one may use the expression, or the maximum values attained by the single systoles, is still more considerable; in severe narrowing they very commonly exceed the original maximum by two or three times its value. The intracardiac pressure reaches its greatest elevation at the moment when the arterial curve rapidly falls. At this point the ventricle makes what may be described as a series of desperate efforts, marked by long excursions corresponding with the heart-beats, which are now slow and rapidly become irregular. This does not last long, it is true; for the intracardiac pressure falls after a very short time whether the ligature be relaxed or not. If an extreme degree of stenosis be maintained, the intervals between the heart-beats become longer and longer, and the curve acquires the closest resemblance to the last part of the curve of asphyxia. If, on the other hand, the passage through the pulmonary be freed, a fall of pressure in the right heart takes place *pari passu* with a reascent of the femoral pressure; whereby the systolic excursions continue large at first, but quickly regain their original size and frequency.

If, instead of the pulmonary, the aorta ascendens be ligatured, the course of the experiment is in all essential particulars the same. Here also, the arterial and venous pressures are wont to remain a very long time completely unchanged, despite the steadily increasing narrowing of the aortic lumen, till at last the sudden and steep descent of the arterial curve and the rapid ascent of the venous pressure ensue. Henceforward the femoral curve proceeds in a straight line, uninterrupted by respiratory- or pulse-elevations, and steadily approaches the abscissa, while the level of the venous manometer rises slowly but continuously. But when the aortic ligature is relaxed, the femoral pressure instantly shoots up, almost always in the first instance above its original level, which it, however, reassumes after the lapse of about five to ten seconds; while the venous pressure is restored in a very short time to normal. Nevertheless, as compared with stenosis of the pulmonary, there are some peculiarities in the details which are worthy of being recorded. In the first place, there may occasionally be seen, sometimes preceding, sometimes following, the abrupt fall, an equally abrupt ascent of the arterial curve, never lasting long, it is true, but very soon giving place to the final descent already described—without doubt the effect of acute anæmia of the brain, which produces, as you are aware, intense excitement of the vaso-motor centre. Moreover, in the aorta the earliest beginning of the gradual stenosis does not manifest itself, as was the case in the pulmonary, by an increase of intracardiac pressure; the twist given to the ligature-rod must be somewhat more ample before the heart reacts to it—to be explained, I think, by the circumstance that a slight diminution of the lumen of the aorta is of no importance when compared with the sum of the resistances normally opposed to the emptying of the left ventricle. But when once the heart's action is affected, the increase in intracardiac pressure is much more considerable, not only absolutely but relatively, than on the right side; so that I have repeatedly observed an ascent of maximum pressure to four times the value of that obtaining with a free aortic channel. Of surpassing interest, however, is the influence of the stenosis of the aorta on the character of the individual cardiac contractions, and thereby on the arterial pulse. The narrower the aortic lumen and the higher the intracardiac pressure, *the more ample do the single contractions become*, and the greater, consequently, the distance between the systolic summit and the diastolic depression of each pulsation. At first no more time is consumed by these enlarged cardiac contractions than formerly; but when they exceed certain limits, they cannot bly be carried out unless more time be expended on the single contractions; or, in other words, as soon as the stenosis has attained a certain pitch, the heart-beats become considerably more ample, but also *slower, less frequent.* A change of this kind must naturally have its effect on the arterial curve, and it may in fact be observed that, after a certain amount of twist has been given to the ligature, the systolic elevations of the femoral become fewer, and, to compensate for this, a good deal larger and less steep in their ascent; *there is an infrequent and sluggish, but mostly elevated pulse.*

These experiments need no further elucidation. They verify in the most convincing way conceivable the correctness of the opinion with which we set out when instituting them, namely, that the work done by the healthy heart increases in the same ratio as the demands upon it. Moreover, no complicated mechanism is required to effect this; for the increase of resistance at once directly excites the heart to more powerful, and therefore more effective, contractions. In the case of the left ventricle, it is conceivable that the greater pressure under which the blood enters the coronary arteries in our experiment, may have a share in increasing the work done by the heart; yet since the right heart behaves in precisely the same way as the left, this factor can only be of subordinate importance. Not till now was it possible for you to perceive how perfect the mechanisms are, by means of which the physiological heart is able to accommodate itself to its tasks. The severity of the stenosis may be increased indefinitely, and the resistance be in consequence enormously intensified; but the work done by the heart keeps pace with it, and despite the stenosis, the quantity of blood ejected at each systole is the same as previously, so that the arterial and venous pressures are maintained at their normal value. And so completely is the place of the heart as the servant of the circulation dependent on its working in this "most advantageous" fashion, that when the resistance becomes so considerable that the cardiac contractions are no longer capable of completely overcoming it, *the circulation is instantly at an end. An intermediate state* where the blood-stream, though not quite normal, continues; where at each systole the heart still throws a certain quantity of blood into the arteries, though not the former normal average amount, and thus maintains the arterial and venous pressures at levels lower and higher respectively than is normally the case ; such an intermediate state, that is to say, as we became acquainted with in connection with increased pericardial tension, *does not exist here.* The physiological heart-muscle can meet the demands on its work, or it cannot meet them ; in the former case, we have a regular physiological circulation, in the latter, death.

But however remarkable this feature may be, for us the chief interest of experimental stenosis lies in the circumstance that it affords the key to the comprehension of cardiac pathology. For you will certainly have no hesitation in utilizing the experiences gained here, not merely in artificial insufficiency of the aorta, but also in the natural valvular and other lesions which impose on the heart an abnormal amount of work. If, in the previously normal aortic valves of individuals advanced in life, or in younger individuals, after an inflammatory process leading to adhesion of the valvular segments has run its course, a pure, uncomplicated aortic stenosis be developed as the result of a high degree of calcification of the segments, the condition produced is not to be distinguished in any essential particular from our artificial narrowing except by its much more gradual establishment, its chronic character ; this, however, is a circumstance, which certainly cannot be anything but serviceable to the discharge of the work of the heart. Yet we are not left to infer from experimental evidence alone that the human heart reacts to the pathological valvular lesions simply by increasing the work done ; we have, in addition, an infallible proof of this in *the increased bulk, the hypertrophy* of the heart, or of that portion of its musculature at least, on which the lesion in question throws a larger amount of work. You all know from every-day experience, that a muscle which has an unusual amount of work to accomplish, increases in bulk, provided it can master this work without rapidly becoming fatigued. On the other hand, *except work,* there exists no normal or pathological factor which is capable of bringing about in a muscle an increase of bulk beyond the natural limits of its growth. In particular, neither hyperæmia, no matter what its origin—unless it be a functional hyperæmia, one *i. e.* with which a stronger excitation of the muscular fibres to contraction goes hand in hand—nor an increase in the nutrition of the organism can effect this. Of course the individuals, in whom muscular hypertrophy is to take place, must be sufficiently well nourished, in order that new material may be formed and built up; in very reduced, debilitated and ill-nourished persons fatigue of the muscles specially exerted would set in much too rapidly to allow of the accomplishment of the larger amount of work for any considerable length of time together. The absence of hypertrophy in a muscle would not therefore exclude the possibility that great demands had been made on its powers; but, having once established that a true hypertrophy, *i. e.* an increase in the number and thickness of the muscular fibres, exists, you may conclude, with absolute certainty, *that this muscle has executed for a considerable period a more than average amount of work.* This, however, is the general rule in all the pure valvular lesions, &c., when uncomplicated by any other severe disease, and holds good on even to advanced age.

We shall first consider in this aspect the various *lesions occasioning an increase of resistance.* In *synechia pericardii*, the entire heart, the right as well as the left side, must do more work, since it has to overcome by its contraction the additional resistance presented by the external adhesions; in fact, there is found, as a rule, a hypertrophy of the whole organ. Not so in narrowing of the cardiac ostia. In stenosis of the arterial orifices, the ventricles hypertrophy, stenosis of the pulmonary artery being accompanied by an increase in bulk of the right ventricle, stenosis of the aorta by a similar increase of the left. Should the right auriculo-ventricular orifice become narrowed, the right auricle hypertrophies; if the left auriculo-ventricular ostium be similarly affected, not only does the left auricle hypertrophy, but, for reasons previously given, the right ventricle also. The hypertrophy takes place, you see, in precisely those portions of the heart, whose evacuation is opposed by the abnormal resistance, and upon which consequently the labour of overcoming this abnormal resistance in addition to the normal one is thrown. The behaviour of the heart is quite similar in *valvular insufficiency*, where the increased demand on its work is occasioned by an addition to the quantity of blood to be set in motion by the contraction of one or more of its divisions, the resistance continuing as before. The hypertrophy is found in the walls of those cavities, which are engaged in the propulsion of the increased quantity of blood; in aortic insufficiency, in the left ventricle; in pulmonary insufficiency, in the right ventricle; in insufficiency of the tricuspid, in the right auricle; and, lastly, in insufficiency of the mitral, in the left auricle and ventricle, and, on account of the increased resistance to the pulmonary circulation, in the right ventricle as well. Yet an additional circumstance supervenes to complicate the case of insufficiency. The filling of a chamber of the heart with a larger quantity of blood can plainly be effected only by an unusual stretching of its walls and dilatation of its cavity in diastole; whereby it is quite immaterial whether the cause of the over-fulness be, as in irritation of the vagus, a lengthening of the interval between two following systoles, or, as in valvular insufficiency, the addition to the normal stream of one proceeding in a false direction. But where such immoderate distension occurs repeatedly, it becomes to a certain extent stationary, as is the case with all cavities enclosed by flexible walls, for example, the urinary bladder and the stomach. Now, that a cardiac cavity should be more than usually dilated during diastole is not in itself pathological or disadvantageous to the circulation; for since the quantity of blood entering the organ varies in accordance with the state of the organism, it is no more possible to lay down an absolutely normal standard for the dimensions of a cavity of the heart than it is for the work done by the heart-muscle. When the pulse of an individual affected with ordinary catarrhal jaundice falls in frequency to about fifty per minute, the arterial pressure remaining quite normal, the heart must, for weeks together, undergo an amount of distension during diastole very considerably greater than before the icterus set in; and yet it will occur to no one to speak of a morbid dilatation of the cardiac cavities here. A dilatation becomes pathological, only when the systolic contraction is no longer capable of so reducing the dimensions of the cavity in question that the portion remaining unemptied shall not exceed the normal limits;—and this quantity, it may be added, is much less in the ventricles than in the auricles. Where the heart-muscle is in other respects intact, everything depends *on the relation of the size of the cavity* to the transverse section of the muscular fibres enclosing it, *i. e. to the thickness of the wall;* those dimensions of the cavity which are physiological for a thick-walled ventricle, may be pathological when the ventricular wall is thinner. But however true this is, the fact remains that, in the various valvular insufficiencies, the continued excessive over-filling leads to *the development of a permanent dilatation of the corresponding cavity;* and we stated only a moment ago which cavities will be affected. In this fact is to be sought the explanation of the difference subsisting between the enlargements of the heart in pure stenosis and in valvular insufficiency; for, while in the former the hypertrophy is simple, in the latter it is accompanied by dilatation, and constitutes what is known as *excentric hypertrophy.*

While then the simple and excentric hypertrophies are nothing but the result of the continuous performance of an excessive amount of work by the corresponding divisions of the heart, their full significance will be apparent from the fact that they alone *make it possible for the heart to continue to meet the demands upon it.* Our experiment showed us that the dog's heart is each moment in a position, despite a very considerable increase of resistance, to eject at its systole into the arteries the quantity of blood required to maintain the high arterial pressure. Undoubtedly the human heart would also be capable of this; and every arduous mountain-ascent or other forced muscular exertion teaches that our heart is easily able to considerably surpass its ordinary performance. But the mountain-ascent is succeeded after a relatively short interval by a period of rest, of recovery, not merely for the voluntary muscles, but also for the heart; the pathological stenosis is, on the other hand, a permanent condition, which makes uninterrupted and abnormally large demands on the working powers of the organ; and the latter certainly cannot, any more than the other muscles of the human body, sustain without fatigue the continuous execution of a maximum amount of work. Exhaustion is prevented by the hypertrophy of the muscle in question. For since the mechanical performance resulting from a muscular contraction increases with the cross-section of the muscle, it is possible for a hypertrophied heart to execute continuously the same, or even more work, than a heart of normal thickness can accomplish for a brief period by its maximal contraction. In what manner the permanent augmentation of the mechanical performance of the heart, rendered possible by its hypertrophy, secures the maintenance of an essentially normal circulation—*i. e.* of such an one as best serves the needs of the economy—in presence of the oft-mentioned valvular lesions, will be most readily understood on a brief survey of the individual cases.

In total synechia of the pericardium, it is the resistance offered by the ribs, diaphragm, &c., that constitutes the abnormal impediment to be met by the systole; the hypertrophied muscle overcomes this resistance, and there is still sufficient energy remaining for the ejection into the arteries of the contents of the ventricle. With no less readiness does the hypertrophied ventricle overcome the abnormal resistance presented by stenosis of an arterial orifice. For the more powerful muscle is capable of forcing in the same time through a small opening as large a quantity of blood as can a weaker through a wide one; and since a greater velocity will be imparted to each particle of blood by the contraction of the thick muscle, the normal quantity of blood reaches, as the case may be, either the aorta through the stenosed aortic orifice, when the left ventricle has undergone hypertrophy, or the pulmonary arteries through the stenosed pulmonary orifice, by means of the hypertrophied right ventricle. Stenosis of the right auriculo-ventricular ostium, which is mostly insignificant, can be compensated at least partially by the hypertrophy of the right auricle; while in the much more important and severe stenosis of the left auriculo-ventricular orifice, the obstacle is met not merely by the hypertrophy of the left auricle but above all by an increase in the volume of the right heart. Cardiac hypertrophy has a precisely similar regulative action when associated with insufficiency. Since, namely, the hypertrophied ventricle throws into the artery at each systole an amount of blood equal to the normal stream entering from the auricle *plus* the reflux from the artery, this latter quantity may be indefinitely increased, and yet the same blood-quantum reaches the arteries in the interval between the commencements of two succeeding systoles as where the valvular segments are capable of closure. In insufficiency of the tricuspid, assistance is up to a certain point afforded by the hypertrophy of the right auricle. In the so commonly occurring insufficiency of the mitral, there is, in addition to the hypertrophy of the left auricle, a similar condition of the right heart. The hypertrophied right ventricle then communicates such an impulse to the circulation through the lungs that there flows from the pulmonary veins into the auricle, and thence into the ventricle during each diastole, an amount of blood equivalent to the quantity which in normal fashion is ejected into the aorta *plus* that regurgitating in a defective manner into the left auricle during systole. The discharge of this abnormally large quantity into the aorta at the next systole is provided for by the hypertrophy of the left ventricle.

The maintenance of an absolutely typical circulation, such as exists where the heart is healthy, is, it is true, more than the hypertrophy can always effect in presence of these lesions; deviations from the normal remain, which are not to be set aside even by the most perfect compensation. Many are indeed occasioned by the compensatory hypertrophy itself. This applies especially to the peculiar condition of the pulse, characteristic of some of these cardiac lesions. In severe *aortic stenosis*, as we were able to determine in our experiment, the cardiac *pulse-rate is retarded*, and the single pulsations sluggish; and although the normal tension of the arteries proves that there is no diminution in the quantity of blood thrown into the aorta at each systole, yet in this form of valvular disease the *pulse-wave*, especially in the more peripheral arteries, remains *low*, because, during the relatively long time occupied by the systole, a comparatively large amount of blood can flow off into the capillaries. The behaviour of the arterial pulse in *aortic insufficiency* is still more characteristic. For since a larger quantity of blood than normal is here ejected into the aorta at each systole, the systolic distension of the arteries must also be abnormally great; on the other hand, the reflux during the next diastole of a certain amount of blood from the aorta into the heart must be attended by a more or less considerable exaggeration of the diastolic recoil of the arterial walls; *i. e. the difference between the crest and the depression of the wave is increased.* The over-stretched arterial wall recedes with remarkable rapidity and to a surprising extent; the pulse becomes jerky, *celer;* phenomena which, as might be anticipated, are more pronounced the greater the excentric hypertrophy of the ventricle. But a still more interesting anomaly of the circulation is sometimes observed in aortic insufficiency, namely, a rhythmical pulsating flow into and through the capillaries, a genuine *capillary pulse.* That the rhythmical acceleration of the blood-stream does not normally proceed beyond the small arteries, but gives place in the capillaries to a uniform flow, is chiefly due, as you are aware, to the elasticity of the arteries and to their resistance. Since, owing to the latter, a constantly increasing portion of the tension is gradually consumed on the road from the heart to the capillaries, the variation of pressure produced by the ventricular systole is incapable of exercising an influence on the blood-stream in the terminal portions of the small arteries, especially when the cardiac contractions follow each other rapidly, as is normally the case. The resistance in the arteries remaining as before, this condition may be altered if, as in aortic insufficiency, the systolic elevation of pressure be specially great. In circumstances, particularly, where the cardiac pulse-rate is from any cause retarded, the rhythmical, jerky flow may extend as far as the capillaries and the commencement of the veins. This occurrence will evidently be favoured by a relatively low tension of the arteries, and by a somewhat diminished elasticity of the arterial walls, which itself again is a result of the incessant excessive distension by the pulse-waves. There may, lastly, be mentioned a third phenomenon, of the nature of a pulse, not occurring in connection with the arteries, but proceeding as a retrograde wave from the heart along the veins, and constituting the true *venous pulse*. It arises in organic or in relative *insufficiency of the tricuspid*, also in insufficiency of the mitral when the auricles communicate by a widely patent *foramen ovale*, and travels backwards through the veins, till the wave is stopped by the closure of their valves; *i. e.* it may be seen in valveless veins and in those whose valves have become insufficient, a condition only too often met with when these vessels are abnormally dilated. In contradistinction to the presystolic venous pulse formerly described (p. 27), we have here a wave of greater vital energy, which may readily be detected at each *ventricular systole* by the finger placed on the internal jugular vein. Simultaneously with it, a pulsatory elevation of the liver may as a rule be clearly distinguished.

The abnormal phenomena displayed by the pulse are of less importance to the well-being of the organism than are some other disturbances of the mechanism of circulation, more or less constantly observed in connection with some of the oft-mentioned cardiac lesions. I have not now in mind those general derangements of the circulation which are wont to appear so regularly and so rapidly in the train of affections of the right auriculo-ventricular orifice; for the want of ability on the part of the right auricle to do more than partially effect the compensation of these lesions by its hypertrophy affords such a simple explanation of the facts, that we are justified in dispensing with their further discussion here. But even where the disease of the valves is compensated as fully as possible, certain anomalies may persist in one or other division of the vascular system. Nor are these irregularities by any means unimportant. To begin with, there is the *over-filling of the pulmonary circulation in stenosis of the left auriculo-ventricular orifice*: for although the hypertrophy of the right heart may after a time secure that a sufficient quantity of blood shall be directed through the narrowed ostium into the left ventricle, the disturbance of the pulmonary circulation, *i. e.* the abnormally high pressure under which the blood must flow through the lungs, will not be remedied thereby. The pulmonary vessels, especially the thin-walled capillaries, become stretched and permanently dilated—a change which will take place more readily in the lungs than elsewhere, since the capillary network is, of course, free towards the alveoli, and in any case receives no support from the surrounding tissue. But the walls of the larger vessels, arteries as well as veins, very commonly suffer under the abnormal pressure to which they are constantly exposed; *thickening* and *sclerotic conditions* appear in the *intima*, as well as fatty degeneration of the endothelium and connective-tissue substance, and lastly, fatty degeneration of the muscularis. Furthermore, the ventricular hypertrophy not uncommonly leads to changes in the heart itself; for, under the influence of the abnormally high internal pressure, *pressure-sclerosis* and *atrophy of the sub-endocardial layer of muscle*, in particular of the *musculi papillares*, may arise here. This condition is most frequently observed in excentric hypertrophy of the left ventricle. I have already dwelt on the effect which the peculiar character of the flow in aortic insufficiency must exercise on the elasticity of the systemic arteries in those cases precisely where the lesion is fully compensated; the *elasticity of their walls is diminished*, and the result very often is a *dilatation* of these vessels, especially of the *arch of the aorta*, combined as a rule with sclerotic changes in the vessel-walls. Lastly, it is very obvious that the powerful variations of pressure in aortic insufficiency cannot long continue to be a matter of indifference to the blood-stream through the vascular area first exposed to them, namely, the *coronary arteries*; yet we are still much too ignorant of the characters of the coronary blood-stream to define more precisely the influence of these variations upon it.

The anomalies not conducive to the advantage of the circulation, remaining over after the fullest compensation, are sufficiently numerous, as you see. Nevertheless the essential factors on which the regularity of the circulation depends are so well maintained that we are undoubtedly justified in speaking of a complete *compensation of these valvular lesions*. For the mean arterial pressure is kept at a normal elevation, the venous pressure is minimal, and the result is that the velocity of the blood-stream remains precisely the same as in healthy individuals; so that if, as is of course assumed, there be no agency at work which is capable of influencing the constitution and circulation of the blood in a morbid direction, it is impossible to see why all the organs of the body should not perform their functions properly. And yet, however true all this may be, you will not delude yourselves into supposing that individuals with a well-compensated cardiac lesion occupy a situation at all comparable to that of persons whose heart is perfectly healthy. We found the criterion of a healthy heart to consist in an ability to accommodate itself with equal perfection to moderate and to large demands upon it; so that when an especially high claim is made on the organ from any side, say the voluntary muscles, this is not rejected but met; and existence is thus physiologically maintained, till, on the cessation of these abnormally high demands, the work to be performed by the heart is again the customary amount. Now the valvular lesions in some measure make such abnormally high demands on the heart, not, however, for a time, but permanently; and it is the office of the hypertrophy to secure that these shall be continually satisfied. But no more is thereby guaranteed. The uninterrupted call made by the valvular lesions is so great that the entire muscular power of the heart is necessary for its satisfaction; should a fresh demand be added, the organ is powerless to meet it. Under ordinary, average conditions of life, with the body at rest, a moderate indulgence in food, &c., the hypertrophy enables the heart to maintain a regular circulation, despite the presence of the valvular lesion; but the working capacity of the organ is unequal to severe physical exertion or to any other kind of increased call upon it. Accordingly the condition of persons with a thoroughly compensated valvular lesion is precisely similar to that of the individuals previously described, whose heart (although its energy is diminished as compared to the normal standard) suffices for the maintenance of a regular circulation under ordinary conditions, but is no match for immoderate physical exertion. A step further, and we have the case of those whose hearts are unable to meet even the demands of ordinary life. But before entering on the discussion of the state of the circulation with the heart in this condition, it may perhaps be advisable to take into consideration another group of cardiac lesions which, it is true, present the utmost contrast to the valvular diseases just described as regards the history of their origin, yet with respect to their pathology have many points in common with these lesions,—I mean the *idiopathic cardiac hypertrophies.*

Such a designation, I need hardly say, would be absolutely unscientific, were it really intended to express that in these cases the heart has increased its volume independently of some cause, in a measure spontaneously. For, since there is not, up to the present, the least ground for believing that any condition occurs in the heart, comparable to the hypertrophy (Riesenwuchs) of an entire extremity, we adhere to the view that *this organ,* like every other muscle in the body, *increases through work alone;* and having determined the existence of hypertrophy in an individual, we shall have to direct our efforts exclusively to the discovery of the cause whereby the heart has been excited to unusual exertion. We have just discussed a group of cardiac enlargements of easy solution—that depending on valvular lesions, &c.; we shall very shortly become acquainted with a second group, likewise extensive and considerable, which is referable to diseases of the vascular system, whether of the greater or lesser circulation, that give rise to increase of resistance. None of the hypertrophies so originating would, now-a-days, be classed by anyone with the idiopathic, in which group many of them were formerly unhesitatingly placed, at a time when their true causal relationship was as yet unrecognised. But there remains over and above these a number of cardiac enlargements, in which the most painstaking scrutiny of the entire body fails to disclose any anatomically demonstrable cause; for such cases the name "*idiopathic cardiac enlargement*" is still in use, and may be retained with a conscious limitation to designate the absence of any observable anatomical cause. The occurrence of, so to speak, functionally conditioned cardiac hypertrophies, cannot in the least excite our surprise, since we have repeatedly and emphatically pointed out how, by reason simply of the varying activity of the various bodily functions, the work thrown upon the heart is so unequal. We may say that whatever raises the arterial pressure or increases the quantity of blood entering the heart during diastole adds to the magnitude of the task to be accomplished by the heart-muscle at the systole. And both these points will be our legitimate guides in investigating whether a lasting and abnormal influence is exerted on the heart by any kind of functional agencies.

In this respect, as has been repeatedly dwelt on, *muscular exertion* stands pre-eminent. For since every considerable muscular effort causes an augmentation of the work of the heart, the conclusion is obvious that the heart-muscle will increase in volume on frequent repetition of such efforts, just as do the voluntary muscles. True, the matter is not so simple here as where a valvular lesion exists. After perforating the aortic valves in a rabbit or dog, the animal acquires, in the course of a few weeks, an excentric hypertrophy of the left ventricle, precisely as does the human being with aortic insufficiency; for obvious reasons, this kind of proof must, in the present case, be dispensed with. Nevertheless, the evidences for such a connection have become so numerous, more especially during the last decade, since special attention was directed to these relationships, that doubt appears no longer admissible. The individuals in question are almost always engaged in arduous callings, involving the daily employment of excessive muscular efforts, such as smiths and locksmiths, sailors and porters, wine-growers, &c.; in such persons there are gradually established the unmistakable signs of a cardiac hypertrophy without the pre-occurrence of valvular or of pericardial disease of rheumatic or other character. For its establishment a very long period, it may be several years, is, as a rule, required; yet the cases communicated by Fräntzel* and others, where hypertrophy of the heart has developed in soldiers after frequently repeated forced marches, show that under certain circumstances a short time is sufficient. This hypertrophy, the result of exertion, affects primarily the *left ventricle*. It is, moreover, regularly associated with dilatation, owing to the overloading in diastole of the cardiac cavities—the inevitable concomitant of an increase in the velocity of the blood-stream. It will be apparent that this condition must very quickly bring about an excentric hypertrophy of the *right* chamber as well.

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* O. Fraentzel, 'Virch. Arch.,' lvii, p. 215.

Although we can satisfactorily establish the connection between strenuous muscular exertion and the consecutive cardiac hypertrophy, there is another group of enlargements of the heart, to which Traube* during the last years of his life directed attention, where our physiological knowledge permits a much less degree of certainty, namely, the hypertrophies arising in consequence of *an immoderate consumption of food and the luxuries of the table.* It is an indisputable fact that the symptoms of hypertrophy of the heart are not infrequently developed in persons between forty and fifty years of age as the result of such excess, and, just as in the case last discussed, without the intercurrence of any special cardiac disease. The individuals in question are generally men in easy circumstances, with well-nourished bodies, who, leading at other times an easy and comfortable existence, consume chiefly during the season their abundant dinner seasoned with a variety of wines. Occasionally, however, the subjects are respectable middle-class citizens, inclined to corpulency and accustomed to plentiful meals and the enjoyment of large quantities of beer. Yet to an accurate comprehension of the manner in which superabundant meals increase the work of the heart, the physiological data at our command are, as has been said, inadequate. At any rate, what has up to the present been suggested by way of explanation, consists essentially of nothing more than observations, more or less vague, as to passive or active over-filling of the portal system, and has little of the nature of genuine insight into the condition of the circulation under such circumstances. We must content ourselves, however reluctantly, with the fact that, even after an ordinary meal, during physiological digestion, the blood-pressure is somewhat raised, and, in consequence, the activity of the heart somewhat increased; and shall, without any desire to forestall the more exact recognition of the causal connection, look upon the immoderate meals as mere abnormal augmentations of influences ordinarily increasing the work of the heart. Possibly, as Traube supposed, the abundant use of spirits and tobacco plays a part here, although observations derived from other sources, in particular on the consequences of the *abusus spirituosorum*, a practice which, nevertheless, is but too frequently indulged in, do not appear to lend confirmation to the view.

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* Traube, 'Ges. Abhdl.,' iii, p. 159. Cf. further Fraentzel, 'Neue Charité-Annalen,' v, 1880, p. 313.

Physiology leaves us wholly in the dark with regard to *cardiac hypertrophies of nervous origin*, for though the influence of stimulation or paralysis of certain nerves on the *frequency* of the cardiac contractions has been the subject of much study and is sufficiently well known, the data telling in favour of a direct action of the nerves on the *energy* and *vigour* of the heart-beats are up to the present scanty. And yet experiences gained from pathology permit not the least doubt that such actions must take place. Take, for example, the so-called *nervous palpitation*, characterised, as is well known, by attacks of hurried or irregular contraction of the heart, of which the patient becomes conscious through a painful and very troublesome throbbing and beating sensation in the breast, often extending to the head and other parts of the body. In these cases the heart-beats are not merely subjectively more perceptible to the patient than normal; it is usual for the cardiac impulse to be objectively strengthened during the attacks, so that often the entire of the front of the thorax is shaken by it, and the pulse is correspondingly full and tense—all this in individuals maintaining perfect quiet, who, moreover, lead a thoroughly rational existence, and whose heart, except during a paroxysm, behaves and performs its functions in an entirely normal fashion. Further, that remarkable aggregate of symptoms known as *Basedow's disease*, and comprising in typical cases *palpitation of the heart*, *enlargement of the thyroid*, and *exophthalmos*, is undoubtedly dependent on disturbances of innervation. The occasional absence or temporary disappearance of one or other of these symptoms makes just as little against the unity of the malady as against its nervous character. With regard to the morbid symptoms connected with the heart in this disease, here, too, not only is the frequency of the cardiac contractions often increased to an unusual extent, but there is a decided accession to their vigour, as shown by the very forcible impulse elevating the wall of the thorax, and by the brisk pulsation of the carotids; although at the commencement of the affection there is no observable augmentation of the volume of the heart. Moreover, the existence of *vaso-motor neuroses* must not be forgotten. These are characterised by the occurrence, over more or less extensive vascular areas, of a diminution, originating in nervous influence, of the calibre of the arteries, which of necessity increases the arterial pressure and thereby the work of the heart. In short, there is no want of evidence for the occurrence of a morbid increase in the work of the heart of nervous origin, and this being the case, we may regard the development of true cardiac hypertrophy of nervous origin as nothing more than the simple result of such increase; as a matter of fact it is not uncommon for excentric hypertrophy of the entire heart to set in in the course of long-continued *morbus Basedowii*, an hypertrophy which may disappear on recovery. If, however, the aggregate of symptoms in Basedow's disease be not insisted on as characteristic of the malady, and stress be laid rather on the disturbance of innervation, we shall certainly not err in interpreting a number of cases of so-called idiopathic cardiac hypertrophy as due to this affection. Whether many of the enlargements of the heart which have of late been often observed to occur *hereditarily*, or at least repeatedly, in certain families, should not be classed under this head (the nervous), is a point well deserving more thorough investigation.

Directing our inquiries to the condition of the circulation in individuals with idiopathic hypertrophy, or as it is also called, *cor bovinum*, we are struck by the very notable contrast to the deuteropathic hypertrophy, already discussed. For in the latter the hypertrophy is compensatory of a valvular lesion; *i. e.* it enables the circulation to continue normal, as if the heart were of normal volume, and the function of the valves unimpaired, &c. In the idiopathic hypertrophies there is no such call for compensation; the valves are all in working order; there is no hindrance which, acting on the organ from without, might prevent the employment of its entire energy in the propulsion of the blood; and thus the increase in volume of its musculature must necessarily have effect on the flow. Without doubt, the hypertrophied ventricle throws its contents into the arteries with greater force than before, it communicates to the blood a greater velocity than before. Whether this is actually advantageous in point of tension and velocity to the blood-stream as a whole will obviously depend on the arrival in the ventricle of a larger quantity of blood during diastole. Should the quantity undergo no increase, the contents of the ventricle will indeed be discharged more quickly into the arteries, the arteries themselves will be more rapidly distended by the blood-wave, in a word, there originates a *pulsus celer*. But there will be no increase in the amount of blood thrown into the arteries, simply because there is no more blood at the disposal of the ventricular systole. The velocity of the blood-stream will also remain unchanged since the supply of blood to the heart from the veins is the same as formerly, and by consequence the flow into the veins from the capillaries and from the arteries into the latter must continue as before. Not so when the ventricle is in a position to receive an abnormally large amount of blood during diastole. A larger object is now presented to the heart of increased functional power, and a larger quantity of blood will be ejected into the arteries at each systole. As the necessary result of this, the *mean arterial pressure will continue to rise* till the amount flowing off into the capillaries during the interval between two systoles is again equal to that thrown into the arteries by a single contraction. With this elevation of mean arterial pressure there must, however, take place, *pari passu*, a fall of tension in the veins, from which an abnormally large amount of blood is being emptied into the heart.

It will be clear without further comment that in cases of hypertrophy with dilatation, so-called *excentric hypertrophy*, the circulation must actually undergo an alteration of this kind, since the ventricle may here be filled in diastole by an abnormally abundant supply of blood; and since at least the great majority of all idiopathic cardiac hypertrophies are excentric, a reply to the question in non-excentric hypertrophy has chiefly a theoretical interest. Still, the same condition obtains in these simple enlargements of the heart. Since, namely, the wall of the ventricle though hypertrophied is distensible, there is nothing to prevent the propagation of the more energetic impulse, of the acceleration of velocity, which the more vigorous action of the heart has communicated to the stream of arterial blood, on into the veins, so that the blood shall pour more rapidly during diastole into the ventricle, which for its part offers no resistance to the entrance of a more abundant supply. Accordingly the arterial pulse is wont to be large, very tense, and incompressible in individuals with idiopathic cardiac hypertrophy; *the arterial pressure is higher and the venous pressure lower than the normal mean standard, and the velocity of the blood-stream is in consequence increased.* It need hardly be added that the pulmonary circulation fully participates in the acceleration.

But however pronounced may be the difference between the circulation in such persons, and in those with fully compensated valvular lesions, it would yet be a mistake to suppose that the former are much better situated than the latter. To say nothing of the dangers to the heart and arteries arising from the high arterial pressure, of the inevitable interference with the expansion of the left lung in inspiration in consequence of the considerable increase in the volume of the heart, leaving out of account too the partial impediment presented to the movements of the diaphragm, it must be borne in mind that the hypertrophy is confronted by a task of abnormal severity, the increased functional capacity by an increase of the demands upon it. Just as the increased demands were the original cause of the hypertrophy, so it is the hypertrophy alone that makes their continued satisfaction possible. The soldier could not sustain his daily marches, nor could the hod-carrier or the smith discharge his laborious occupation, were it not for the occurrence of hypertrophy; the gourmand too, would be forced to succumb to the large quantities of food and drink consumed by him, nor could the heart in Basedow's disease maintain the frequency and force of its beats for weeks and months together. The features are essentially the same as those presented by the compensatory hypertrophy of valvular disease—with one point of difference it is true, namely, that the excessive calls upon the heart in valvular disease are absolutely continuous, unintermittent, while in labourers and in gourmands they are interrupted by intervals of rest. Still so long as the occupation or manner of living is persisted in, these intervals, during which the work of the heart more than meets the needs of the economy, are of short duration; and a possible advantage to the organism as a whole, springing out of the increased functional capacity of the heart, cannot be seriously admitted, unless the enlargement of the heart continue after the abnormal conditions have disappeared, *i. e.* after the adoption of a moderate and quiet mode of living or the removal of the disturbances of innervation. The hypertrophy is not permanent, however; on recovery from *morbus Basedowii*, on relinquishing the pleasures of the table or the laborious occupation, as the case may be, *it becomes gradually retrogressive.* An enlargement of the heart, which continued in the absence of all cause, *i. e.* without any unusual demand on the work of the heart, would be idiopathic in a literal sense, and such an hypertrophy does not and cannot exist. For the rest, such retrogressive change in a cardiac enlargement is not often met with by the physician; for, as a rule, the patients come under observation only when it is already too late, when the disease has taken that unfavorable turn which is alone necessary to the complete correspondence of the picture with that occurring in the non-compensated cardiac lesions.

I have in the foregoing discussion endeavoured to make it quite clear, on the evidence of facts derived from physiology and pathology as well as from experiment, how exquisitely our heart is adjusted to respond to the calls upon it, from whatever side these may come. The work to be accomplished by the heart under ordinary vital conditions, in the absence of fatigue and with a temperate mode of living, falls far short of that of which it is each moment capable. Indeed, its functional capacity, its contractile power, is so great that it may, on the one hand, suffer considerable reduction, and yet continue to meet the ordinary average demands upon it; while, on the other hand, the calls upon it may be in the highest degree augmented without exceeding its power of satisfying them. And the heart can do so not merely for a short period; it can continuously respond to really exorbitant demands, effecting this by the aid of the muscular hypertrophy which, under the influence of these demands, becomes established in an appropriate position. Who will venture to say where the limits of this functional power lie? That such limits exist is self-evident, so that I need only remind you of our experimental stenosis, in which, after a certain amount of twist had been communicated to the ligature-rod, the heart was no longer able to overcome the opposition of the abnormal resistance. You know what occurred then; despite the most vigorous efforts, the heart could not prevent an immediate fall in arterial pressure to an extent no longer compatible with life. That in human beings too, sudden death may result from similar causes, I have no doubt. Moreover, many cases are on record, in which the complete severance of an entire valve has rapidly brought on the fatal issue; and in those cases of excessive exertion, where, for example, a porter suddenly falls dead under a heavy burden, the causal connection must often be the same.

Such occurrences are, however, extremely rare; and did no other danger threaten the patient suffering from heart-disease, he would have little cause for anxiety. Nor, apparently, is there reason to fear that a chronic valvular lesion may, through progressive contraction or calcification, reach such a pitch of severity that the functional power of the heart can no longer keep pace with it. The gradually increasing stenosis is accompanied by a gradually increasing hypertrophy, and if the moderately thickened muscle were capable of overcoming the abnormal resistance of moderate degree, the ostium, though very much narrowed, will oppose no insuperable obstacle to the extreme hypertrophy. Yet one point must be constantly borne in mind, namely, that this extraordinary and admirable functional power *is possible only w* [illegible] *art-muscle* in all other respects *intact:* and ho [illegible] ments must be fulfilled before the integrity of the heart-muscle can be described as perfect! The ganglia and muscle-fibres must not only be morphologically and chemically intact, but also absolutely physiological in point of excitability; and with respect to the circulation through the coronaries, not only must it be free from impediment but the blood itself must be of normal constitution and temperature. Now, we have already considered the manifold processes by which the cardiac musculature may suffer alterations of structure and composition; we have also made mention of those hindrances to the circulation, which so frequently attend sclerosis of the coronary arteries. In accordance with our plan, we shall postpone the more detailed consideration of the alterations in the composition of the blood; the more so as we do not need to treat of them at length here, since they are of only secondary importance in cardiac pathology; it is at most the anæmic conditions, which, in so far as they impede the absorption and supply of oxygen to the heart-muscle, exercise an unfavorable influence on the function of the latter. The maintenance of a normal bodily temperature is certainly of much greater importance to the functional capacity of the heart. For not only is the frequency of the contractions accelerated by an increase in the temperature of the blood, but *every extensive deviation from the normal bodily temperature reduces the irritability of the cardiac ganglia and promotes fatigue of the heart-muscle.* Considerable alterations in the temperature of the blood, whether by gain or loss of heat, act so powerfully and promptly in this respect, that death by *paralysis of the heart* may be occasioned with extreme rapidity. When, as in ordinary fevers, the changes are not so severe in character, their effect becomes more apparent *the longer they persist.* Possibly, in many diseases attended by pyrexia, but more especially in septic and numerous other infective fevers, the effect on the heart may be still more strengthened and accelerated by the direct poisonous action of the specific causes of disease; at any rate a rise of blood-temperature of some duration alone suffices to diminish more and more the working capacity of the heart-muscle. The impossibility of becoming acquainted directly with the condition of the muscle-fibres, to say nothing of the ganglion-cells, and the want of a reagent which would make it possible to judge from the heart *post mortem* whether the excitability of nerve- and muscle-fibre has been physiological *intra vitam*, is, it is true, a misfortune that, apart from fever, repeatedly forces itself on our attention. Yet this cannot prevent our doing full justice to the observations made on the living subject. According to these, it is incontestable that nervous influences, whose paths we are not always able to trace, are capable of influencing the heart's action injuriously; and whatever the intermediate tract may be, it is by no means unusual in the experience of the physician for severe *depressing emotional disturbance* to prove itself capable of permanently and very considerably prejudicing the functional power of the heart, especially if the organ be already diseased. Lastly, to the changes in the heart, unrecognisable by our reagents and optical contrivances, must be added one, which in pathology is perhaps the most important of all, namely, *fatigue* and *exhaustion*. I am alive to the fact that this is a point where the secure foundation of physiological experiment is wanting. In a normal condition, the diastole following each contraction appears amply sufficient constantly to secure the heart from all fatigue. But who will guarantee that this shall also suffice when opposed to an abnormal increase of work, *i. e.* if the heart accomplishes at each systole a task very considerably above the normal? This, however, we have seen to be the case in the various cardiac lesions, and that despite the presence of hypertrophy. In the absence of the latter, fatigue would very rapidly set in; but can the hypertrophy always avert it? Yes, if we had the guarantee that the heart of individuals with compensated cardiac lesions should never be called on to accomplish more than the measure of work to which the organ had adjusted itself. Bear in mind, however, how manifold are the conditions by which the claims upon its energy may be occasionally, if only temporarily, augmented. Consider, further, how, for example, with every increase in the frequency of the pulse the periods of recuperation for the heart-muscle in diastole are diminished. This would be a matter of indifference to a healthy heart; is it so where the organ is compelled constantly to strain its powers to the very uttermost in order to satisfy the continuous demands upon it? Add to all this that there remains in such patients, despite the most perfect compensation, a number of anomalies of the circulation, which do not contribute to the advantage of the latter or of the remaining organic functions, and which sooner or later must assert themselves in some way or other. It need, I think, excite no surprise, should a moment ultimately arrive when the overstrained organism strikes work, even without the occurrence of any fresh complication of importance. I should like to see the term "*fatigue*" applied exclusively to such a course of events, whether it affects the nervous or the muscular apparatus of the heart. Such cases are by no means rare, so far as can be inferred, at least, from the very large number of cardiac lesions coming to the knowledge of every pathological anatomist, where no disease of the myocardium can be detected by the most painstaking examination, although the clinical history and the remaining *post-mortem* appearances leave no doubt that a disturbance of compensation had taken place *intra vitam*. Occasionally a condition is met with at the autopsies of persons who have suffered from heart disease, which may be regarded as the immediate cause of death, as, for instance, embolism of the middle cerebral, or erysipelas of an œdematous leg; but as a rule nothing more is discovered than the signs or consequences of the disturbance of compensation, œdema, indurations, &c., &c., and we shall mostly seek in vain for anything which might throw light on its cause. There is a widespread belief that the commonest source of failure of the heart is fatty degeneration of the hypertrophied myocardium; yet I am unable to discover the grounds for this opinion. For should the great frequency with which fatty metamorphosis is found in the hearts in question be put forward in its favour, I would be inclined first of all to regard the statements by which the view is supported as decidedly exaggerated; and in the next place, who can tell whether the fatty degeneration of the muscle has really preceded the derangement of compensation and has not made its appearance subsequently as an effect?—on general pathological principles a much more probable idea.

These, then, are the factors by which the energy of the heart-muscle is more or less seriously endangered. A heart, even when perfectly healthy, may be threatened by them; still more one which is already incapable of maintaining an approximately regular circulation except by the continuous expenditure of its entire energy. The simplest example of such peril to the healthy heart is afforded by rise of temperature, whether of pyrexial character, or produced at will by experiment, or caused by insolation. When the bodily temperature has reached an elevation of about 44—45° C, the consequence is, as already stated, cardiac paralysis and death; when, on the other hand, the rise of temperature is less, but persistent, as in many diseases attended by pyrexia, the heart, though enfeebled, can yet for a long time put forth the efforts necessary to ward off the appearance of general disturbances of the circulation; but when the exhaustion has exceeded certain limits, these also set in. Nevertheless this change in the character of the symptoms is usually much more conspicuous if one of the mischievous conditions already described affects a heart whose functional capacity was previously only exactly sufficient for the satisfaction of the moderate demands upon it—in which class, if one choose, may be placed, it is true, the hearts of those who have passed through protracted febrile diseases. It is immaterial in what way the hearts in question have been reduced below the normal standard, whether this be owing to chronic fatty degeneration or other cause capable of giving rise to loss of contractile substance, or be the result of extensive sclerosis of the coronaries; it is immaterial, too, whether the heart be one whose functional capacity is in itself abnormally great, but whose entire energy is at all times consumed in meeting the continuously increasing and abnormally large demands upon it, as, for example, in the valvular diseases and in the so-called idiopathic enlargement of the heart. When, in these cases, one of the injurious influences just mentioned asserts itself, the invariable result is a loss of more energy than can be dispensed without injuring the circulation. What is the state of the circulation under these circumstances?

Let us fix our attention on some one or other of the valvular lesions, *e. g.* stenosis of the pulmonary orifice. From the moment when the energy of the right ventricle no longer suffices to completely overcome the abnormal resistance, less blood than before will be thrown at each systole through the narrowed aperture into the *a. pulmonalis*, and consequently less will pass through the lungs into the left auricle and thence into the left ventricle, so that the aortic system cannot receive the ordinary average quantity at the next systole. Other things being equal, the immediate result must be a diminution in the size of the individual pulsations and *a lowering of the mean arterial pressure*, as has been described with sufficient minuteness in connection with our pericardial experiment. On the other hand, the blood which the right ventricle was unable to discharge into the pulmonary remains in this cavity at the conclusion of its systole, and in consequence the blood of the right auricle cannot enter the ventricle so readily as it otherwise would: and although it may at first effect an entrance owing to the distensibility of the ventricular walls, not merely is the situation unimproved, but rather disimproved, since the too-feeble heart finds itself opposed to an abnormally large blood-quantum: in any case, after a few heart-beats the quantity of blood present in the heart at the commencement of systole has become so considerable as to constitute a decided obstacle, first to the auricle and very shortly to the venous stream as well. This involves *a rise of mean venous pressure*, and in addition of course, for reasons already known to you, a marked strengthening of the venous pulse. The relation between the tensions of the two divisions of the systemic circulation having been in this way reversed, *a decrease in the velocity of the blood-stream* through the capillaries is, as you also know, inevitable, a decrease in which the pulmonary circulation, whose tension was in any case first affected by the reduction, will evidently be implicated.

The sketch of pulmonary stenosis here given you, fully applies, *mutatis mutandis*, to each of those remaining cardiac lesions which are characterised by a disproportion between "demand for work" and "capacity for work;" it matters not whether it be that to normal demands an absolutely inadequate working power is opposed, or whether abnormally increased demands have to be met by a functional capacity which, if at all increased, is insufficiently so. It is obvious that this will apply to insufficiency of the pulmonary valves, where the energy of the right chamber is inadequate to the propulsion of the normal diastolic blood-quantum *plus* that which has regurgitated from the pulmonary arteries; and it is no less applicable to stenosis and to insufficiency of the left auriculo-ventricular orifice, when the motive force of the right ventricle is deficient. Nor can it be otherwise in the lesions of the aortic orifice with imperfect compensation, except that here the reaction on the systemic veins is not direct, but through the medium of the left auricle and pulmonary system; and consequently we have here a sort of intermediate stage with hypertrophy of the right ventricle. True, this is not of much service to the patient; for the motive force of the left ventricle is unaffected by the hypertrophy of the right, and therefore the low arterial pressure and the over-filling of the left ventricle continue; the advantage derived from the hypertrophy of the right ventricle will soon have reached its limits, even though the factor causing the disturbance of compensation be not of a nature to involve both sides of the heart: it is even possible, that the increase in pulmonary tension attendant on the enlargement of the right chamber may, under certain circumstances, aggravate the situation of the unfortunate patient. Moreover, it need hardly be explained that synechia of the pericardium must also bring about this change in the general circulation, when, in presence of the external impediment, the functional power of the heart-muscle is no longer capable of propelling the normal blood-quantum into the arteries. Nor, as has been stated repeatedly, can the case be different, when the motive force of the right or left ventricle has, owing to the formation of indurations or to fatty degeneration or other cause, deteriorated to a degree incompatible with the maintenance of the usual regular circulation. Here, too, we have a low arterial pressure due to diminished supply to the arteries by the systole, and, because of the insufficient evacuation of the ventricles, a resistance to the entrance of venous blood with rise of venous tension, occurring on the right side forthwith, on the left side only after hypertrophy of the which, if at all increased, is insufficiently so. 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Lastly, the idiopathic character of an hypertrophy can occasion no difference in the course of events; for this form too depends in reality, as we have already more particularly shown, on abnormal demands on the work of the heart; and should the latter be continuous, while, on the other hand, the contractile force is reduced, there must of necessity result the same general disturbances of the circulation which accompany all these non-compensated cardiac lesions. At the autopsy of persons who have perished from what is known in England as "*weakened heart*," there is found, instead of hypertrophy, a *dilatation*, often really enormous, of both sides of the heart; yet without any valvular lesion or other anatomically discoverable causal affection.

It is, in all essential particulars, a uniform picture that is presented, when the heart has ceased to accommodate itself to the claims upon it, when the organ has become, as it may be aptly expressed, "insufficient." The details, especially the so-called physical signs, may offer variety enough, the character of the pulse may also vary—I remind you, for example, of the *pulsus celer* in aortic insufficiency, a condition which must naturally be all the more conspicuous, where the arterial pressure is low: but in those points that are decisive for the state of the circulation as a whole, the harmony is very complete. There is, too, an affection of the heart itself that recurs in all cases of cardiac insufficiency, be the original defect or the cause of the failure of compensation what it may, namely, *an enlargement of one or more of its cavities, dilatation.* That such dilatation must take place, will be at once clear to you on calling to mind that it is *the overfilling or excessive distension of the cardiac cavities with blood* which constitutes, in these cases, the obstacle to the entrance of venous blood into the heart, and elevates, at the same time, the venous pressure. In all cases of cardiac insufficiency—if we leave out of consideration stenosis of the tricuspid, soon to be discussed—the *right* ventricle at least must be abnormally dilated; in a large number of cases, such as fatty degeneration or induration of the left heart, idiopathic hypertrophy, lesions of the aortic orifice, the left ventricle must also participate in the dilatation, and may possibly be involved still earlier than the right. Now, dilatation, as a very common complication of hypertrophy, has already been briefly considered, and stress has been laid on its somewhat unimportant character. The dilatations with which we are concerned at present are not distinguished from those merely by their extent; for though it is quite true that the dilatation of the insufficient heart is as a rule more considerable than that associated with hypertrophy, yet the diastolic volume of the ventricle may be extreme in many cases of aortic insufficiency and of idiopathic hypertrophy, and yet no disturbance of compensation result. The pathognomonic element in the dilatation of cardiac insufficiency, or more briefly, the *absolute dilatation*, consists rather, as has been already stated, in a disproportion between the dimensions of the cavity and the motive force of its muscular wall, *i. e.* in *the incapacity of the heart to diminish by its contractions the cavity to the physiological minimum*. It is obvious that when once such a disproportion has made its appearance the dilatation will be constantly progressive and therefore increasingly difficult of removal. From the functional character of the condition it follows, moreover, that its estimation *post mortem* must be attended with the greatest uncertainty. I lately warned you against the danger of coming to a hasty conclusion as to the functional capacity of the heart *intra vitam* from the apparently histological integrity of its muscle; to-day I add a similar warning with respect to the expression of an opinion as to whether you have before you a relative or an absolute dilatation of the heart. There are of course extreme cases that admit of no doubt, where an enormously dilated left ventricle is enclosed by a muscle scarcely a line in thickness; but when, for example, the heart of an individual with aortic insufficiency has stopped in diastole, the left ventricle may appear to be very wide and decidedly thin-walled, although it had adequately discharged its function up to death. In general it may be looked upon as certain that the great majority of those affected with heart disease do not die until a marked disturbance of compensation has taken place, so that you may usually assume the dilatation to be absolute; nevertheless, it will always be well to seek the determining anatomical criteria elsewhere. Thus in insufficiency of the aorta, an excentric hypertrophy of the *right* ventricle affords a much more convincing proof of disturbance of compensation than does dilatation of the left ventricle, however pronounced; and every trace of uncertainty disappears when œdema, nutmeg liver, induration of the spleen and kidney, in short, when in the remainder of the body the signs of severe venous hyperæmia are present.

To sum up our discussion—we set out from the consideration that the work done by the heart in systole is under normal circumstances a very variable amount, being greater or less in proportion to the magnitude of the demands made on the organ by the differing vital conditions. This is possible because the functional capacity of the heart is so much more considerable than the ordinary average vital conditions and the claims upon its work necessitate, so that this capacity may, through a variety of morbid influences, be diminished to no inconsiderable extent, and yet suffice for these average conditions. Again the functional power of the heart is so great that it is possible for it to satisfy claims even of a quite exorbitant character such as far exceed the limits of the ordinary vital conditions; though to meet such demands permanently, an hypertrophy of the whole or a single division of the heart is necessary. But for the maintenance of a circulation which shall be, in spite of these undoubtedly pathological conditions, in all essential particulars normal, the existing contractile substance must be continually strained to the utmost; and the accession of any factor, whatever its nature, which diminishes the energy of the contractile substance, immediately tells on the circulation in such a way that, contemporaneously with the dilatation of one or more divisions of the heart, the arterial pressure sinks below normal, the venous pressure rises above normal, and the velocity of the blood-stream decreases. These are the broad features, which, it is true, may present the utmost variety in individual cases. In one individual advanced in life, the myocardium may be the seat of extensive indurations as a result of sclerosis of the coronaries, in another, calcification of the semilunar valves may give rise to severe stenosis of the aortic orifice—yet both persons continue perfectly well, because in the former the portions of the heart-muscle still unimpaired, in the latter the enormous hypertrophy, suffice for the maintenance of a regular circulation. Thus years may pass till at last the old man falls a prey to a pneumonia or a bronchitis with fever or a bad attack of enteritis, and after a short time the signs of cardiac insufficiency with œdema, changed urinary secretion, &c., make their appearance. Or, there may arise in a young woman the subject of a severe rheumatic fever a marked acute insufficiency of the mitral. Only too rapidly a high degree of dyspnœa sets in, her urine becomes scanty and red-coloured, her hue cyanotic, the liver swells and the legs are the seat of considerable anasarca. Gradually, however, as the fever subsides, the state of the patient improves, the œdema disappears, the urine becomes more plentiful, the face assumes a more natural hue ; and though, as is very possible, some dyspnœa still remains, she can, provided her habits are prudent and quiet, lead a perfectly contented existence, and attend to her household duties. On going upstairs, it is true, she will be troubled now and always with shortness of breath, but the inconvenience is only temporary ; she passes through a couple of pregnancies without any drawback, and all goes well till she is attacked by a puerperal fever : in a short time all the typical symptoms of cardiac insufficiency are again present. But the patient recovers from this attack also, and again leads for years a perfectly supportable existence, although the loud systolic murmur audible at the apex and the intensified second pulmonary sound prove only too clearly the permanence of the mitral disease. Finally, however—perhaps when the woman has lived to be sixty—the right ventricle gives way to gradually increasing fatigue and exhaustion, and there is developed anew that fateful and this time fatal aggregate of symptoms, to which the patient after protracted and painful suffering succumbs. In a third case, it is sad and depressing emotions that impair the compensation, so far excellent; while in another, the failure of compensation dates from enormous physical exertion—exertion that, had the heart been normal, might perhaps have been attended with worse, possibly immediately fatal, results, but which in the hypertrophied organ has occasioned a considerable loss of contractile power, it may be by immoderate stretching or even rupture of its muscular fibres: to cases of this kind the designation "overstrain of the heart," as proposed by Fraentzel* might be appropriately applied.

But whatever be the cause of the disturbance of compensation, it cannot have escaped you that its effect on the circulation in general differs in no essential particular from that resulting from the abnormal increase of pericardial tension. In fact, to anyone who bears in mind the intimate interdependence of the two phases of the heart's activity it cannot appear the least strange, that the imperfect action, whether of the suction-pump or of the force-pump, should in its consequences to the circulation amount to one and the same thing. The reason why, in spite of this, the lesions of each category cannot be identified the one with the other, is to be sought in the important fact that disturbances involving the machinery of the force-pump can be compensated to an astonishing degree by increasing the motive-power of the pump. While the motive-power of the heart continues unimpaired it is hardly possible for lesions of any character to interfere with the performance of the force-pump; the regular work done is immediately dependent on an adequate measure of motive-force, and stands or falls with this. But against anything that deranges the action of the suction-pump the motive-force of the heart is of little avail. For even though the suction-power of a very muscular ventricle is incontestably greater than that of a weak one, yet an actual impediment to the flow from the veins into the heart can hardly arise out of this relationship; and at any rate it will be very insignificant as compared with the impediment resulting from increase of pericardial tension. But since the greater or less energy of the heart is of no importance in tension of the pericardium, the object of the physician's treatment cannot in such cases be to add to this energy, but solely to remove the factor increasing the tension, *i. e.* the lesion itself. It is precisely the contrary in derangements of the force-pump; for the primary disease is here as a rule incapable of correction, so that the aim of the physician must be to maintain the motive-force of the heart in such a condition as shall render the complete compensation of the lesion possible.

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* Fraentzel, Neue Charité-Annalen, vi, 1881, p. 275.

From the point of view of this contrast between imperfections of the suction- and those of the force-pump, a special interest attaches to a further variety of cardiac lesion, which has so far received only passing notice, namely, disease of the *tricuspid valve.* Affections of this valve are, it is true, uncommon; as has already been stated, stenosis is to be classed with the greatest rarities, and insufficiency, while indeed coming much more frequently under observation, is mostly associated with severe mitral or aortic disease, so that an opportunity of estimating the isolated affection rarely presents itself. But, however small their practical importance may be, they are theoretically noteworthy, inasmuch as *they combine the peculiarities of the lesions of both categories.* In so far as they damage the force-pump we have considered them already, and have dwelt on the fact that it is the *hypertrophy of the right auricle* which compensates the prejudicial effects of the lesion. But the right auricle furnishes only a fraction of the energy employed in conveying the blood from the systemic veins into the right ventricle, and another source of power, such as that presented by the right ventricle in maintaining the circulation through the pulmonary veins, does not exist here. Consequently, lesions of the tricuspid are also, as has been said, imperfections in the suction-pump, and the heart is accordingly almost incapable of effecting their compensation. We observe, as a matter of fact, in *insufficiency of the tricuspid,* despite the hypertrophy of the right auricle, a vast retrograde blood-wave passing back into the venous system at the very moment when the contents of the latter should be poured most plentifully into the heart. It is obvious that the escape of blood from the veins must be impeded thereby, even though the rise of mean venous pressure is usually kept within moderate limits; this being due to the circumstance that the backward movement of the blood-wave is barred by the nearest closing valves, and that, during the succeeding ventricular diastole, the large veins, being abnormally distended, drive their contents toward the heart with a corresponding increase of force. *In stenosis of the tricuspid* the venous stagnation will be still more considerable; so extreme, indeed, that this valvular lesion, unlike all others, proves after a short period without exception destructive to the general circulation, and, by reason of its absolutely incurable character, is more pernicious even than are pericardial exudations of large volume.

Another factor in the cardiac activity which has so far received hardly a passing notice, must now be minutely discussed; I refer to the pulse-rate, the *frequency of the heart's contractions*, whose accurate consideration you will already have noticed has not formed part of the foregoing exposition. We should properly commence by investigating if the processes already described, whether impairing or not the work of the heart, *exercise* at the same time *any influence on the frequency of the heart-beats, and if so of what nature*. But if you reflect here, how manifold are the agencies controlling the frequency of the pulse, the impossibility of establishing a definite relationship of dependence between those processes and the pulse-rate will soon be apparent. The latter results, as is well known, from (1) the action of the *intracardiac* centre, also called the cardiac musculo-motor nerve-centre; (2) the action of the *vagus*; and (3) the action of the *accelerator nerves*, distributed to the heart by the sympathetic. Powerful stimulation of the cardiac ganglia not only strengthens the cardiac contractions but quickens the pulse-rate; stimulation of the accelerator nerves has the same effect; while irritation of the vagus, as is well known, diminishes the frequency of the heart-beats. The inhibitory centre is in a condition of permanent excitation, so that any enfeeblement of it has a substantial influence on the pulse-rate, a factor absent from the accelerator. Assuming, now, that in an individual with imperfectly compensated mitral stenosis, these various nerves are not acted upon from any other side of the organism, that in other words, all remaining influences maintain a state of equilibrium so that the normal mean frequency of the pulse would be the result of their action; how will the number of heart-beats in the unit of time be affected by the cardiac lesion in such a person? You know that the pressure in the left ventricle and the arterial pressure in general are lowered below normal in uncompensated mitral stenosis.

Consequently (1) the wall of the heart is less distended and its internal surface less strongly stimulated—hence *slowing* of the pulse-rate; (2) but the vagus-centre, of which the blood-pressure is a natural exciter, is also more feebly stimulated—hence *quickening* of the pulse-rate; (3) the decrease in the velocity of the circulation, which, as you know, accompanies the cardiac lesion, leads to a less active exhange of gases in the lungs, and the blood becomes abnormally rich in carbonic acid; but an increase in the quantity of carbonic acid contained in the blood produces strong irritation of the vagus-centre—therefore, again *slowing* of the pulse-rate; (4) should the centripetal, sensory nerves of the internal surface of the heart be excited by the excessive distension of the left auricle and by the diseased condition of the mitral itself, and a reflex be communicated thence to the accelerator—the consequence is *acceleration* of the pulse; (5) clinical observation has repeatedly shown that in fatty degeneration of the heart the pulse-rate is slowed, presumably because the usual stimuli are here inadequate to set up a contraction; should therefore, as often happens, a fatty degeneration of the heart-muscle complicate the mitral stenosis, we have here a factor capable of *decreasing the rate of the pulse.* But what holds good in stenosis of the left auriculo-ventricular orifice might be shown to apply to the other cardiac lesions, and it will accordingly be evident to you without further comment that, as I already indicated, *a constant relationship between the cardiac lesions and the frequency of the pulse does not exist.* The frequency of the heart-beats is increased or diminished according as one or other of the factors in question preponderates; or should all of them unite in maintaining the equilibrium the pulse-rate continues normal. But in particular it will excite no surprise that the frequency of the pulse should at different periods vary extraordinarily in one and the same case of cardiac disease. Moreover, if we consider that nutrition as a whole suffers in consequence of the cardiac lesion, so that the constitution of the blood must be gradually altered, and that this change must react on the excitability of the nervous apparatus; if we call to mind in addition that the ganglionic centres as well as the heart-muscle are exposed to fatigue and exhaustion during the progress of morbid processes in the heart; there can be no difficulty in accounting for the frequent appearance, especially in advanced stages of the disease, of the most pronounced irregularity in the rhythm of the cardiac contraction, an *arhythmia* of the pulse. If Heidenhain* was able to show that in perfectly strong and healthy dogs a considerable rise of arterial pressure makes the heart-beats arhythmical, because the cardiac and inhibitory nervous systems are disproportionately excited, and that after chloral-poisoning even a moderate rise of pressure has the same effect, we can certainly experience no surprise at such an occurrence in persons suffering from heart-disease, where the excitability of the nerve-centres is subjected to disturbing influences of the most varied kind.†

As we have seen, a constant relation of dependence between cardiac lesions and the frequency and rhythm of the pulse does not exist; hence the other side of the question, or *the manner in which alterations in the frequency of the pulse affect the circulation*, may lay claim to greater interest. You know that under normal conditions the number of heart-beats is by no means the same in all individuals, that it is subject to a variety of fluctuations according to the age or sex or size of the body of an individual, as well as to the period of the day, and that it is moreover every moment extremely susceptible of variation; psychical influences, muscular activity, digestion, nature of the respiration, and many other agencies tell on the cardiac pulse-rate in one or other direction. While we have here to deal with alterations of transitory character, there are some diseases in which most marked and persistent changes in the frequency of the pulse arise, of course through the agency of one of the nervous mechanisms already mentioned. Everyone knows that the pulse-rate is increased in fever; that it is, on the other hand, decreased in icterus; while the effect produced in the latter case by the salts of the bile acids, is induced, in intracranial tumours and basilar meningitis, by pressure on the vagus-centre. What is the state of the blood-stream in presence of these sometimes excessive alterations in the frequency of the cardiac contractions?

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* Heidenhain, 'Pflüg. Arch.,' v, p. 143.

† Traube, 'Ges. Abhdl.,' iii, p. 47, 183. Nothnagel, 'Deutsch. Arch. f. klin. Med.,' xvii, p. 190. Marey, 'Trav. du Laborat.,' 1876, p. 307. Sommerbrodt, 'Deutsch. Arch. f. klin. Med.,' xix, p. 392, xxiii, p. 542. Knoll, 'Arch. f. exper. Path.,' ix, p. 380. Rosenstein, 'Berl. klin. Wochenschr.,' 1877, No. 20.

The opinion that the velocity of the blood-stream increases with the acceleration of the cardiac pulse-rate, and decreases with its retardation is not confined to the laity alone. Nevertheless, the very variations which are in this respect even normally apparent should by their extent have thrown doubt on the conclusion. Moreover, irritation of the vagus when not excessive teaches that a moderate slowing of the pulse-rate exerts absolutely no influence on arterial and venous pressure, and by consequence none on the velocity of the blood-stream. Indeed, the means resorted to by the organism for the regulation of the effects attendant on the varying frequency of the pulse are extraordinarily simple. They depend essentially on the circumstance that in these alterations in the pulse-rate it is not the duration of the single systoles but of the *diastoles* that is altered; where the pulse is rapid the latter become shorter, where slow, longer. If now the frequency of the pulse is decreased, the ventricle receives in diastole a more abundant supply of blood, so that the next systole can eject so much more into the arteries; if, on the other hand, the pulse-frequency is increased and the second systole succeeds the first with abnormal rapidity, an abnormally small quantity of blood flows from the veins into the ventricle in the interval, and the amount of blood thrown into the arteries by the latter is diminished. But if either a proportionately larger quantity of blood be thrown into the arteries fifty times, or a proportionately smaller quantity a hundred times, it is evident that these vessels will be just as well filled as if the normal quantity were thrown into them seventy times. It is here presupposed, of course, that the muscular power of the ventricle, *i. e.* its motive force, is normal. Should it be diminished, the ventricle is not in a condition to cope successfully with the large quantity of blood that has flown into it during the prolonged diastole; it is possible, indeed, that it may fail to communicate the necessary impulse even to the small quantity entering it when the diastole is curtailed. On the other hand, an hypertrophied ventricle will be capable of compensating a very considerable degree of retardation of the pulse, especially if it be also dilated; and, then, if the frequency of the pulse is increased, it will actually raise the arterial, and lower the venous, pressure, and thus accelerate the blood-stream. For the blood flowing from the auricle—at first, it is true, a small quantity owing to the short duration of the diastole—will be driven with greatly increased velocity into the arteries by the hypertrophied ventricle; and after this has occurred a few times, the acceleration will be propagated on into the veins also, out of which, during the ventricular diastole, the blood will now flow with increased rapidity. The shortness of the diastole is then compensated for by the acceleration in the movement of the blood, so that a moment soon arrives when the normal quantity of blood flows into the ventricle at each diastole, despite its brief duration. But if the same quantity of blood be transferred from the veins to the arteries a hundred instead of seventy times per minute there results a rise of tension in the latter and a fall of tension in the former, and the velocity of the blood-stream is in consequence augmented—a result which need not ensue on an increase in the frequency of the pulse, were the motive-force of the heart normal.

You see, everything hinges upon the *motive force* of the heart, upon the strength of the contraction of the heart-muscle. But it has already been shown that a heart, whose motive force is diminished, must bring about a lowering of mean arterial pressure, and that, on the contrary, a heart, whose muscle works more powerfully than normal, must cause a rise of the same; thus an alteration in the frequency of the pulse can merely somewhat accentuate or soften-down the effects of these factors. In fatty heart the arterial tension will be low in proportion as the cardiac contractions are infrequent; in hypertrophy of the left ventricle it will be the more considerable the greater the frequency of the pulse. On the other hand, the circulation in an individual with *cor bovinum* will be little accelerated if the rhythm of the heart-beats be slow.

These considerations perfectly accord with the fact already mentioned that feeble or moderate stimulation of the vagus gives rise to no change of blood-pressure whatever. Nor has section of the vagi, after which the pulse increases considerably in frequency, any effect on the blood-pressure; no more has stimulation of the *n. accelerans*, although this quickens the pulse-rate from 20 to 30 per cent. In jaundice, too, the radial artery is not by any means readily compressible; provided no other noxious influence capable of affecting it be present, its mean tension is, as a rule, normal. With regard to pyrexia, marked, as it always is, by increased frequency of the pulse—here, more than elsewhere, is the importance of the heart's motive-force to the blood-pressure and velocity of the blood-stream apparent. For there are febrile diseases in which the arterial pulse is hard, full, and large; and others where, the tension being inconsiderable, the pulse is soft and easily compressible, while the slight cyanotic reddening of the cheeks and lips and the coolness of the extremities clearly point to a slowing of the blood-stream. Thus, if a few grains of fresh pus or of purulent sputum be injected under the skin of a dog, there ensues within a few hours a rise of rectal temperature of two or even three degrees; if the carotid be now connected with the kymograph, you observe a curve of remarkably low mean pressure, and at the same time very low and, by way of compensation, more numerous pulse elevations.* Again, Paschutin,† experimenting in Ludwig's laboratory, observed, on exposing dogs to the elevated temperature of a hot-air chamber, that measurement of the blood-pressure in the carotid showed, as a rule, a not unimportant rise coincident with the increase in the frequency of the pulse; this continued till the rectal temperature reached the value of 41·0—41·6° C., when on still further heating, a rapid fall of pressure in consequence of cardiac paralysis made its appearance. Hence it can no longer seem strange to you that in numerous cases of extreme acceleration of the pulse due to causes other than increased temperature of the blood, as, for instance, the nervous palpitation of chlorotic, anæmic individuals, and in many examples of Basedow's disease, the pulse should be but little distended, small, and weak, while at other times in attacks of palpitation it presents characters the very reverse of these. For you know that one and the same heart may work with different degrees of energy at different periods, and the height of the blood-pressure and rapidity of the blood-stream are far more dependent on this factor than on the frequency of the heart's contractions.

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* Heidenhain, 'Pflüg. Arch.,' v, p. 107.

† Paschutin, 'Ber. d. Math.-Phys. Kl. d. Leipz. Ges.,' 1873, p. 95.

Accordingly it will appear to you superfluous to describe in detail how in the various cardiac lesions the circulation is influenced by alterations in the frequency of the pulse. Here too the criterion must be—is the effective work of the heart altered by the cardiac lesion or not; and if so, is it augmented or diminished? I have already emphatically stated that a moderate pulse-rate or one still slower is the desideratum in hypertrophy. In the compensated cardiac lesions, on the other hand, it is certainly always best for the circulation that the pulse-rate should be normal and the rhythm regular. Should you, on the other hand, be inclined to suppose that a moderate acceleration of the pulse-rate might be to a certain extent beneficial in cardiac lesions without compensation, I will not altogether dispute this, but will merely remind you that a heart which contracts a hundred times in the minute will without doubt be more readily fatigued than one which does not contract oftener than sixty or seventy times. Moreover, you will at once perceive that in stenosis of the cardiac orifices it must be a sort of relief to the blood-stream when the heart-beats follow each other slowly; for the normal amount of blood can pass through the narrow ostium, even without an increase in the velocity of the flow through it, provided only a sufficient time be allowed for its passage.*

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* The most important contributions to the pathology of the heart are those of Traube, 'Gesammelte Abhandlungen,' Berlin, 1874—1878. Other sources of information are the well-known treatises on diseases of the heart by Stokes, Friedreich, Bamberger, v. Dusch, and Rosenstein. The sketch of heart-disease by O. Rosenbach in Eulenburg's 'Realencyclopädie' is well weighed and interesting, though the author is somewhat given to theorising.

CHAPTER II.

CHANGES IN THE TOTAL PERIPHERAL RESISTANCE.

Importance of the arterial resistances to the circulation.—Their regulation.—Elevation of the total resistance by tonic contraction of the small arteries.—Stenoses and dilatations of the aorta and pulmonary artery.—Sclerosis of the arteries.—Impediments to the pulmonary circulation.—Rise of pressure in the thoracic cavity.

Consequences to the circulation.—Compensation by strengthening the heart's work, or cardiac hypertrophy.—Failure of compensation.

Diminution of the total arterial resistance.—Consequences to the circulation.

After having hitherto devoted ourselves to the study of the effects which disturbances of the normal cardiac activity exercise on the blood-stream, we now turn to the second factor co-operating in carrying on the circulation, namely, the vessels. The importance to the circulation of the vessels, when these are in a normal condition, *i. e.* perfectly intact as regards their physical and chemical constitution, does not simply consist, as is well known, in their presenting prescribed channels to the blood-stream; for they influence very essentially the pressure and velocity of the latter by means of contrivances making it possible for them to oppose a greater or less *resistance* to the flow of the blood. You are acquainted with these contrivances; they are the *elasticity of the vessel walls*, and above all the *muscular apparatus* forming part of the structure of their coats. The quantity of blood contained within the vessels is, as we now know, far from sufficient to [illegible] all the available space so as to produce even a moderate tension of the vessel-walls.* In fact every artificial injection of an animal or human subject teaches how much more liquid can be taken up by the blood-vessels than is normally contained in them during life; and, on comparing the ears of a rabbit after dividing the cervical sympathetic of one side, you will again and again be struck by the enormous difference observable in the state of fulness of the vessels on each side, which simply signifies that the vessels of the ear ordinarily contain a much less quantity of blood than they can accommodate. It is obvious that, if the blood is to flow under considerable tension through any part of a vascular system so imperfectly filled, this can be effected only by the interpolation of special resistances which shall act by opposing the blood-stream through that part. That the elasticity of the arteries is not competent to maintain by its resistance the arterial pressure at a high level we are taught by the operation of dividing the cervical cord, or even the splanchnics in the rabbit; for although the elasticity of the arterial walls cannot have suffered in any way by this procedure, you at once perceive an enormous fall in the pressure of the carotid.† It is pre-eminently the narrowing of the small arteries by the contraction of their circular muscular coats that renders the escape of the blood from the aorta difficult, and thus imparts to the arterial blood-pressure that elevation which we estimate in the carotid by means of the manometer. Wherever this constriction due to muscular action is absent or very inconsiderable, as is the case in the pulmonary arteries, there the blood-pressure is very low. It must be admitted that the hypothesis of a permanent tonic and unvarying contraction of the circular muscular coat of the systemic arteries, such as was not long since universally assumed to exist, cannot at present be adhered to; for we now know, owing chiefly to the researches carried on in Ludwig's laboratory, that the greatest variations are constantly presented here, that one and the same artery is now wide, now narrow, and that, corresponding with this, the resistances in the same vascular area vary to a great extent. Nevertheless, in a normal condition the different areas of the vascular system are so associated that the constriction of one branch artery shall be coincident with the dilatation of another, and that consequently *the sum of the resistances which each moment oppose the flow from the aorta shall be maintained at the same value.* This is the origin of the high mean tension of the arterial system as contrasted with the much lower tension of the venous system, in which the blood on its way to the heart has to overcome very trifling resistances, and it is to this difference of pressure that the flow from the arteries to the veins, tending to equalise the tensions, is due. Since, however, the rate of this equalisation, *i.e.* the velocity of the flow in the capillaries, depends *cæteris paribus* on the amount of the difference of pressure between arteries and veins, it is evident that a certain degree of disparity is necessary in order that the normal velocity of blood-stream through the capillaries shall be maintained, and that consequently the *total resistance* opposing the efflux from the aortic system must not fall below a certain value, which we therefore call the normal. But it must not, on the other hand, exceed this value, since the heart cannot normally overcome more than a certain resistance by its contraction; and consequently there is the danger lest, owing to the resistance being greater than normal, the systole may not be in a position to discharge as much blood into the aorta as passes through the capillaries into the venous system in the interval between this and the succeeding systole.

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* Dogiel, 'Ber. d. Leipz. Gesellsch. Math. Phys. Kl.,' 1867, p. 200.

† Asp, ibid., p. 131.

However essentially important the amount of resistance prevailing in the vascular system accordingly is, maintaining as it does the normal mean pressure, and the mean velocity of the blood-stream, the organism has itself, as I reminded you just now, the means of regulating its economy in presence of these varying resistances; it effects this by securing simply that when the resistances in one portion of the vascular sectional area are diminished through dilatation, they shall in another portion be increased by contraction, and vice versa. A compensation of this kind can, it is obvious, occur only in those portions of the tube-system that are branched, where, therefore, each individual tube allows the passage of a part only of the blood present in the entire sectional area in question; it cannot occur in those places where the tube-system is simple, *i.e.* in the aorta and pulmonary artery.

Such compensation will be equally impossible, when, in place of the aorta or pulmonary, the whole of the peripheral sectional areas unitedly experience a change of resistance; and it will be also impossible, or at least extremely difficult, when not the whole indeed, but very extensive portions of the united sectional areas involved, are altered in this way. It will be advisable, accordingly, to examine next, what is the effect on the circulation of alterations of the resistance in those vascular areas through which the entire or almost the entire quantity of blood passes in its circuit, *i.e. of alterations of the total resistance in a cross-section of the vascular channel.*

A possibility will probably at once occur to each of you as being the simplest by means of which the resistance of the vascular cross-section may experience an abnormal *enhancement*, namely, the *increase of tonic contraction in the small arteries*, such as is known to follow to an almost universal extent whenever the vaso-motor centre in the medulla oblongata is somewhat powerfully excited. That the resistances are really considerably augmented is proved by the rise of arterial pressure indicated by the manometer in the carotid, &c. True, it does not follow from this that the resistances are increased in all parts of the cross-section; it has indeed been shown in Heidenhain's* laboratory that, during reflex stimulation of the medulla oblongata, the vessels of the skin and muscles not only do not participate in the narrowing, but are supplied during the stimulation with a larger quantity of blood than when the medulla is not stimulated. Yet the rise in carotid pressure proves that the compensation afforded by this dilatation of the vessels of the skin and muscles is imperfect. You know too how the organism proceeds to deal with this rise of pressure produced by extensive arterial contraction; the vagus is first irritated by the elevation of blood-pressure and thereby the pulse-rate slowed for the time being; above all, however, the *n. depressor* passing to the medulla from the heart is excited by the increased demands on the latter, and this at once brings about a remission in the arterial contraction, whereby the original condition is re-established. At least it is certainly re-established, when the cause of the more vigorous action of the vaso-motor centre in the medulla has meanwhile ceased to operate. In pathology this cause is most frequently the overloading of the blood with carbonic acid. Since, however, many morbid processes exist by which the aëration of the blood in the lungs is permanently interfered with, we are quite justified, I think, in raising the question, how does the circulation behave under such circumstances; the more so as the possibility of explaining certain conditions, which have not up to the present been successfully interpreted, may perhaps be thus opened to us. I have now in mind those cases, of course uncommon, in which, amongst the consequences of extensive and firm pleuritic adhesions, further of chronic bronchitis, and of the advanced stage of processes marked by contraction of the lung, an hypertrophy not only of the right but *of the left heart* is developed, although no obstruction whatever of the aortic system is observable either *intra vitam* or at the autopsy. It seems to me in fact, having regard to the last-mentioned circumstance, that the left ventricle hypertrophies here, because the spastic contraction of the small arteries due to the dyspnœic character of the blood has furnished and continues to furnish considerable abnormal resistances for the left heart.*

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* Ostroumoff, 'Pflüg. Arch.,' xii, p. 219. Grützner und Heidenhain, ibid., xvi, p. 1. Heidenhain, ibid., p. 31.

Whether this view be correct or not, there is, besides this simple quantitative increase of the normal resistances, a whole series of pathological processes that augment the resistance of an united cross-section of the vascular channel *by adding to the normal resistance new abnormal ones.* It is usual to mention as of primary importance (1) *narrowings* and (2) *widenings* of those portions of the vascular system which are simple, *i. e.* of the aorta and the pulmonary artery. Yet the problem presented by these changes in the vascular lumen is not so uncomplicated as current statements might lead one to suppose. With regard to the narrowings in the first place; you will have to take into account that the value of the resistances opposing the blood-stream is, especially in the aorta, already very great of itself, so that we shall not be justified in expecting a marked increase of resistance through narrowing of the lumen of the aorta unless this narrowing is either severe or extends over a large portion of the aortic wall in a longitudinal direction: an annular constriction, involving a short circumscribed spot, by which the diameter of the aortic lumen is reduced two or three millimetres, can evidently exert nothing more than a very trifling influence on the total resistance. Experience proves the occurrence both of *circumscribed* and *general* narrowings of the aorta, both, it is true, only in rare cases. The favourite seat of the circumscribed stenoses is the neighbourhood of the *d. arteriosus;* their length as a rule is limited to 0·5 or at most 1 ctm., but may occasionally be extreme. In the general variety of abnormal narrowing, on the other hand, the change is participated in not only by the aorta but usually by its larger branches as well, so that the circumference of the aorta may not be greater than that of a normal iliac artery, while the section of the iliac does not exceed that of a healthy popliteal. If with this anomaly, which is always congenital, other more general and extensive developmental disturbances be associated at the same time, the former loses thereby *eo ipso* all significance as a factor increasing the resistance for the circulation of this immature and anæmic individual; abnormal narrowness of the aortic system has, however, been repeatedly observed unaccompanied by other derangements of development.[*] Much commoner than these stenoses are encroachments on the aortic lumen by parietal thrombi, which are often enough multiple in this vessel: yet the foregoing reflection is eminently applicable here; for the thrombi can hardly constitute an obstacle worth mentioning to the blood-stream, if for no other reason because the thickness of the deposits does not usually exceed 2 to 3 mm. Moreover, the lumen of the aorta is protected against possible narrowing through the pressure of tumours or, it may be, mediastinal exudations by the high internal pressure prevailing in it and by the considerable pliability of its walls. Stenosis by compression plays, as might be expected, a somewhat greater *rôle* in the pulmonary, while in this vessel nothing analogous to the circumscribed narrrowings of the isthmus of the

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* Cf. Traube, 'Ges. Abhdl.,' iii, p. 127.

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[*] Cf. Quincke, in 'Ziemssen's Hdb. d. spec. Path.'

Dilatations or *aneurysms* of the pulmonary are also to be regarded as the greatest rarities. They are all the more frequent in the aorta, whose ascending portion and arch are especially predisposed to them. Thus if there were really good grounds for the belief that aneurysms occasion a considerable increase of resistance for the blood-stream, the pathologist would have ample opportunity for observing the effects of an abnormal increase of resistance in the unbranched portion of the aortic system. More accurate consideration of the changes in the flow conditioned by an aneurysm does not, however, lead, so far as I see, to this conclusion, it being immaterial in this regard whether the aorta is continued *in toto* into the aneurysm, or whether the latter is seated upon one side of the vessel only. For it is, of course, undoubtedly true that a portion of the motive power normally employed in the propulsion of the blood forwards must, especially in the circumscribed aneurysmal dilatations of the whole circumference of the aorta, be consumed in tearing asunder the particles of blood, *i. e.* in overcoming the internal cohesion of the liquor sanguinis, since this operation is known to take place with the least expenditure of force where the forward-motion is in parallel lines, in a tube, consequently, with unaltered lumen. Neither will I dispute that a very large aneurysm must interfere with the whole circulation by withdrawing from the rest of the vascular system the large amount of blood wasted in filling it. This latter evil is usually remedied in a large measure by the gradual formation of thrombi; but even if they should fail to be formed, this factor can hardly be regarded as capable of raising the total resistance in the aorta to any great extent: and the loss of power sustained in tearing asunder the fluid particles is utterly incapable of effecting it. It cannot accordingly be supposed on *a priori* grounds that the existence of a circumscribed aneurysm, even of really large dimensions, can increase the resistance in the aorta to an appreciable degree, nor does experience contradict our reasoning. At least, after what I have myself seen, I must express my entire agreement with those authors, in particular with A. Key,* who have failed to detect that striking reaction on the heart and whole circulation in pure uncomplicated aneurysms. It is something very different when the endarteritic process, as so commonly happens in these very aneurysms of the ascending aorta, is transmitted from the wall of the aneurysm to the aortic valves, and here brings about a gradually increasing insufficiency ; in such cases, there will of course be established that change by which the heart regularly reacts to the valvular lesion, *i. e.* excentric hypertrophy of the left ventricle.

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* A. Key, 'Nord. med. Arkiv,' i, No. 22.

General dilatation of the whole aorta, in which as a rule the greater number of the remaining large arteries share, is decidedly more important than the circumscribed form, owing less perhaps to the great enlargement of the bed of the stream than to the causes which lie at the bottom of this enlargement. For such general dilatations of the aortic system are very commonly developed in advanced age, owing to the fact that the elasticity of the arterial walls usually begins to suffer little by little and to diminish more or less by reason of the stretching that has taken place without interruption for many years. The consequences of this loss of elasticity to the circulation are obvious : the part played by the elasticity of the arterial wall in the propulsion of the blood ceases more or less to be sustained. Lastly, there may be mentioned in this connection another morbid change, identical with the foregoing so far as its effect is concerned, but in itself of very different nature, although also appearing by predilection in advanced age. This is the group of *sclerotic* and *atheromatous* processes affecting especially the intima, and of *calcareous* deposits attacking both intima and media. For while an inelastic arterial wall cannot amply and promptly contract after distension by the pulse-wave, an inflexible and rigid tube is incapable of being properly distended by it. The aorta is the favourite seat of these sclerotic, atheromatous, and calcareous degenerations, but the arteries of lower order are also sometimes so extensively affected that an abnormal rise in the total resistance of the arterial system is the result.

In the pulmonary circulation, on the contrary, such vascular diseases play an unimportant part. [illegible] very many other processes by [illegible] ar or [illegible] th monary vascular system are rendered impervious; and thus the united sectional area is diminished, and by consequence the resistance increased. To this class belong *induration* of the pulmonary tissue; all sorts of processes terminating in *ulceration* and the *formation of cavities*, having mostly a chronic course; *pulmonary emphysema*, owing to which the capillaries perish by destruction of the alveolar septa in which they are situated; and obstruction of arteries by emboli or thrombi. In a lung, too, which from some cause or other, *e. g. a large pleuritic exudation* or a *pneumothorax marked by high tension*, is compressed and so reduced below its natural volume, a more or less large number of vessels must be occluded and rendered impervious. A special circumstance, however, contributes to make it possible for considerable impediments to the circulation to exist in the lung, although the vessels may be quite pervious. The variation in volume which the lung experiences in the different phases of respiration is, as you know, by no means immaterial to the circulation through it. For the flow of blood into and through the capillaries is very largely promoted, in a normal condition, by the respiratory expansion of the lungs, while during artificial respiration, on the contrary, the entrance of blood into the pulmonary capillaries is impeded at every insufflation, as indicated by the pressure-curve of the *a. pulmonalis*, or rather of course of one of its branches; the contrast being due, as will be readily understood, to the exactly opposite pressure relations in which the pulmonary capillaries are on each occasion placed. It follows from this, however, that in ordinary respiration with the thorax closed *everything which impedes the change of volume of the lungs must be disadvantageous to the circulation through them.* Such an impediment is offered by *total synechia of the two layers of the pleuræ;* not of course because the lungs are now closely applied to the thorax—since this indeed is normally the case—but because the gliding movement of the lungs along the thorax wall towards the abdomen is thus rendered impossible; the transverse diameters of the lungs can, it is true, be increased, but not their vertical dimensions. Immoderate development of the *panniculus adiposus*, as well as of the masses of fat in the abdomen, may also form an obstacle to changes of volume of the lungs; for the muscles of inspiration, especially the diaphragm, are unable to completely overcome the resistances thus originated, and in consequence fail to expand the thorax to the normal extent. *Chronic bronchitis* acts in the same direction, for filling of the bronchi with catarrhal secretion prevents the adequate expansion of those portions of the lung into which they lead; and the same holds good of such parts of the pulmonary tissue as cannot expand sufficiently, and become *atelectatic*, in consequence of some condition or other diminishing the thoracic cavity, *e. g.* kyphoskoliosis of the vertebral column. In the same category may be placed lastly that affection of the lungs characterised by deficient development of its elastic fibre, and commonly known as pulmonary emphysema, although the name used by Traube, "pulmonary enlargement," or *volumen pulmonum auctum*, would more correctly describe the condition present.

All these factors, varying extraordinarily in their nature—we shall have to concern ourselves with them more minutely when dealing with the pathology of respiration—must act the more certainly as increasers of resistance precisely in the pulmonary circulation, since a compensation by diminution of the resistance in the unaffected channels is here out of the question owing to the absence of tonus in the smaller arteries.* The total resistance to be overcome by the work of the right heart must therefore be increased when an impediment is offered to the passage of blood through even small portions of the vascular channel; it is at the same time implied, of course, that this increase will be greater in proportion as the hindrance to the blood-stream through the lungs is more general and extensive.

Finally, the question arises, whether there are any pathological processes that increase the resistance in the *venous system* without any possibility of compensation. These can only be such, as is easily understood, which impede the entrance of venous blood into the heart or at any rate into the thorax. We have already treated the question at length so far as the heart is concerned, and as regards the thorax, everything may be summed up in a few words: *whatever raises the intrathoracic pressure*, whatever, in particular, *changes the*

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* Badoud, 'Verh. d. Würzb. physik. med. Gesellsch.,' N. F., Bd. viii.

negative into positive pressure, must impede the emptying of the veins. This is caused, as you are aware, even in individuals whose lungs are perfectly sound by forced expiratory efforts, for example, coughing; it occurs, moreover, at each expiration in persons whose lungs can be only laboriously diminished in volume on account of obstacles in the air-passages or severe emphysema.

What is the condition of the circulation, we ask, when the total resistance in the vascular system is increased from any of the foregoing causes? The question is not difficult to answer. If it be in the systemic arteries that the resistance is abnormally raised, a portion of the heart's motive force will be consumed in overcoming it, and the remainder will be insufficient to propel the normal quantity of blood at a normal rate into and through the arteries; or, to express it otherwise, the pressure between the heart and the obstacle will be normal, even above normal, but beyond this point it must be lowered in proportion to the amount of abnormal resistance. Accordingly in stenosis of the aorta, and in severe sclerosis and atheromatous degeneration of this vessel, the lowering of pressure must be present in the middle and smaller arteries; in sclerosis of the latter, and still more in narrowing of the small and smallest arteries of vaso-motor origin, it will occur beyond these, *i. e.* in the commencement of the capillary system. In the case last mentioned, the condition of the arteries of the skin and muscles, which not only do not participate in the general contraction, but may even simultaneously dilate, can, as already indicated, operate as a compensating factor, so that now the blood, flowing more rapidly through these vessels, reaches the great veins, and by them the heart. Such compensation is, however, out of the question in all our other impediments to the arterial blood-stream, because these increase the total resistance, because they act on the whole cross section. Here the effect of the accumulation behind the impediment must assert itself as far back as the ventricle, and you know very well what happens now; the *ventricle dilates*, and stagnation in the pulmonary vessels and systemic veins, attended by all those consequences to the velocity of the blood-stream that have been so thoroughly discussed in connection with the uncompensated cardiac lesions, is the result. Nor is it otherwise when the resistance in the pulmonary circulation is augmented. In stenosis of the pulmonary trunk it is self-evident that, on the one hand, too little blood will flow through the lungs into the left ventricle, and, on the other hand, that the right heart, and farther back the systemic veins, must be overfilled. But this appears equally probable of impediments situated peripherally in the lung itself, for if the sectional area of the pulmonary vessels is diminished, the right heart cannot—this is the conclusion immediately forced upon us—send the normal quantity of blood into the left ventricle, and again there will be a fall of arterial and rise of venous pressure. Moreover, it need hardly be explicitly stated that, if the flow of venous blood into the heart be impeded by a positive intrathoracic pressure, this must lead to stagnation in the entire venous system, and secondarily, to lowering of the mean arterial pressure. Should, however, this rise of pressure in the thorax occur only periodically at each expiration, we shall have a rhythmical, jerky flow, especially through the veins in the neighbourhood of the heart, in the neck, &c.—a *rhythmical* movement which here frequently assumes the characters of a complete expiratory turgescence of the veins, provided only the venous system be already overfilled and abnormally distended, as is ordinarily the case in the diseases here concerned.

Indeed, the phenomena last mentioned are never absent, as soon as the pressure in the thorax has become positive. When, on the other hand, no morbid signs are observed in the vessels in connection with other varieties of increased resistance in the systemic or pulmonary circulations, you know how this is to be accounted for. It is the *increase in the work done by the heart*, which here makes its appearance as a compensating factor, precisely as in the cardiac lesions formerly described. Compensation occurs most readily in the pulmonary circulation: for it is clear that, with the inconsiderable pressure normally prevailing here, the contractions need be only very slightly strengthened to overcome this pressure, to distend more forcibly the branches of t pulmonary artery, and to urge the blood with a through them. A series of experiments, Lichtheim* in my institute in Breslau, has afforded really surprising results on this point. When, in a curarized dog whose respiration was artificially maintained, and whose carotid and *v. jugularis* were connected with manometers, the lumen of the left pulmonary artery was completely occluded by means of a strong thread introduced through an aperture in the wall of the thorax, *neither the carotid nor the venous pressure underwent even the most trifling change;* moreover, many of the larger branches of the right pulmonary artery could, in addition, be ligatured, without this having any influence on the arterial or venous pressure. Here, then, more than the half, almost three fourths indeed, of the pulmonary channel, had been rendered impervious, and consequently the united sectional area reduced almost to a fourth part of its normal dimensions, and yet the normal quantity of blood arrived in the left ventricle through the reduced section. This is achieved by means of the simplest imaginable mechanism. The pressure in that portion of the pulmonary system which lies on this side of the interposed resistance, rises in consequence of the resistance, and stretches the pervious branches in such a manner, *i. e.* accelerates the blood-stream so much, that a quantity of blood equal to that formerly passing through the whole of the two lungs, is now hurried in the same time through the quarter still remaining. The rise of pressure is certainly in itself trifling; thus the soda-manometer introduced into a branch of the right *a. pulmonalis* showed, on closure of the left pulmonary artery, a rise from 180 to 260 mm. only, or about 80 mm. soda, equal to 6 mm. mercury, approximately. An increase of pressure such as this would, it is evident, have little or no effect in the systemic circulation, characterised, as it is, by a high degree of resistance; in the pulmonary circulation whose physiological resistance is so slight, it is amply sufficient to bring about an adequate degree of stretching of all the branches still pervious. Consequently the addition to the work of the right heart thus originated is in itself not large, and you will not be greatly astonished that the ventricle is in a position to execute off-hand this slight excess of work. Still it is an excess of work, and thus it is readily intelligible that the ventricle on which the heavier task is imposed will *hypertrophy* when the increase of resistance in the pulmonary circulation becomes permanent. This will naturally occur earlier, and the hypertrophy itself reach a higher pitch the greater the increase of resistance, and especially the more general the impediment to the blood-stream through the lungs, as is the case in severe and wide-spread emphysema, in total synechia of the layers of the pleura, in extensive chronic bronchitis, and all the more readily in these very diseases, as the subjects of them are very often young and in other respects vigorous. I have, moreover, had the opportunity of observing very pronounced hypertrophy of the right ventricle associated with extreme corpulency.

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* Lichtheim, 'Die Störungen d. Lungenkreislaufs u. ihr Einfluss auf d. Blutdruck,' Berlin, 1876.

It would be still less possible for the obstacles in the systemic circulation to be overcome for any length of time without a similar hypertrophy of the left ventricle. But here it is of advantage to the heart that the varieties of increased resistance in question are all of them wont to develop slowly and gradually, or else to form very early, either during embryonic life or very soon after birth; at a time, consequently, more favorable than any other to active growth. I have now in mind the general and circumscribed stenoses of the aorta in the neighbourhood of the *d. arteriosus*, which are in the majority of instances congenital, and are therefore, as regards the history of their development, diametrically opposed to the aneurysmal dilatations of the aorta and arterio-sclerosis, conditions that, for reasons to be discussed later, are emphatically diseases of advanced age, and thereby in the highest degree chronic. Here may be slowly and gradually developed an hypertrophy of the left ventricle sufficient to effect a normal filling of the arteries despite the abnormal resistance, and thus to maintain the pressure and velocity throughout the whole circulation at their proper values. This is the reason that the heart of very old persons does not as a rule participate in the general atrophy of the body, and especially of the muscles, but rather increases in mass and volume.* [illegible] but surely which can be accomplished in old age culty in earlier years when the remaining organs are all vigorously fulfilling their functions. On the other hand, it would be superfluous, after having formerly discussed the point so fully, to lay stress on the fact that the compensation already established may be destroyed by any of those influences that are calculated to depress the functional activity of the hypertrophied heart-muscle, in particular by exhaustion and by fatty degeneration. For the same thing occurs as in the cardiac lesions, and the effects on the circulation which then present themselves are exactly the same familiar ones; *lowering of the mean arterial pressure, stagnation and overfilling of the venous system, and slowing of the mean velocity of the blood-stream.*

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* Perls, 'Der

The *lowering* of the total resistance in the vascular system plays a very unimportant part in pathology as compared with its elevation. For since, if we leave out of account the friction of the blood in the capillaries, it is in the small arteries that the chief resistance is normally opposed to the blood-stream, it will be obvious that, so long as the constitution of the blood remains unaltered, a decrease of resistance can arise only when a relaxation of tonus occurs in all or in a majority of these vessels. This happens, as is well known, when the vaso-motor centre is paralysed or cut off from its connection with the great mass of the vaso-motor nerves by section of the cervical cord. This is, further, the necessary consequence of all circumscribed lesions causing an interruption of conduction in the upper part of the spinal cord, such as compression, laceration, softening, tumours. If the interruption be situated very high up in the first part of the cervical cord, as will be the case, for example, in dislocations of the axis behind the atlas, the vessels of the whole body, except those of the head, relax; the further down the seat of the interruption the larger the portion of the vascular system continuing innervated, and should it not occur until after the n. splanchnici, the vaso-motor nerves for the entire abdominal cavity, have been given off, we can no longer speak of a diminution of the total resistance, inasmuch as the relaxation is then confined to a comparatively small part of the arterial system: we have a *local* but no general disturbance of the circulation. In those cases, on the contrary, where the resistance in the small arteries has actually disappeared throughout the greater part of the body, the effect on the circulation as a whole must be highly important. For should the resistance to the discharge of arterial blood into the capillaries and veins cease, the blood must necessarily pass with great rapidity from the arteries to the veins, and thus the difference of their tensions be very considerably diminished. In that case, however, the rapidity of the blood-stream must decrease excessively, and if the relaxation of the arteries be really very complete, things may even go so far that the veins, on account of the enormous retardation of the stream, soon cease to convey to the heart the amount of blood required for the next systole. But this is nothing short of a *gradual extinction of the circulation*, and that no regulative action is here possible will be apparent without further explanation, especially on considering that the heart, already inadequately supplied with blood, can but imperfectly fill the coronary arteries, and that the deficient circulation through these vessels is a fresh source of weakness to the organ. If, on the other hand, there be no complete paralysis of the arteries, but merely a diminution, not an abolition, of tonus, a circulation will indeed be still possible, yet it must be accompanied by a more or less decided fall of arterial pressure and a corresponding retardation of the blood-stream; a fall of pressure and retardation in which the pulmonary circulation must necessarily participate, although, on account of the absence of all tonus, no change is suffered by the resistances here. That the effects, as regards pressure and mean velocity, of vaso-motor paralysis of any very large vascular area, *e. g.* of the splanchnic, must perfectly accord with the foregoing description, is evident from the nature of the case: we cannot, of course, estimate the special characters of the flow in the various portions of the vascular system, paralysed and not paralysed, before discussing thoroughly a subject to which we now turn our attention, namely, the *local disturbances of the circulation*.

CHAPTER III.

LOCAL DISTURBANCES OF THE CIRCULATION.

Introductory remarks on the physiological means of regulating the calibre of the arteries.

In the last lecture we saw how great an influence is exerted on the circulation by raising or lowering the total resistance prevailing in the vascular system ; such an effect cannot of course be expected where the change of resistance involves, not the entire vascular system, but *single* vascular areas. For I have repeatedly dwelt on the fact that the organism possesses the capacity of compensating a change of resistance in one direction by a second in a contrary direction, and we shall presently become acquainted with the means it employs to effect this end. But although the general blood-pressure and the mean velocity of the blood-stream are not influenced by these local variations of resistance, it is in no way excluded, rather it is to be confidently anticipated, that these changes will be of very material import to the blood-stream through the affected vascular area. In fact the interesting topic, a favourite theme of older medicine, namely, *local disturbances of the circulation*, comes up for consideration here and shall now occupy our attention.

We certainly now-a-days assume a different attitude towards this chapter from that adopted little more than a decade ago. For we now know that even in a normal condition the quantity of blood present in each particular organ is constantly liable to much greater variations than was formerly believed. The reason of this is to be sought in a circumstance to which I have repeatedly alluded in your presence, namely, that the quantity of blood circulating through the body is utterly inadequate to fill all the vessels at once. For such being the state of affairs, it is obvious that an ample and powerful blood-stream, such as is called for during the functional activity of each organ, muscles, glands, skin, brain, &c., is possible only when other areas are imperfectly filled. Nor will the case be altered where from any cause the quantity of blood in the body is increased beyond the physiological standard. For the sole result of this increase in quantity is an increased consumption by the organism, a subject which will be treated in detail in connection with so-called plethora. The blood is not a stable organ; if indeed it can at all be regarded as one, it must be as an organ in a state of unceasing change; fresh blood is being continually formed and old consumed, and the organism is adjusted to maintain only the normal mean amount; should the gains increase, the losses also increase.

There is accordingly a need for other regulative agencies, by whose aid a temporary excess or diminution in the filling of the various vascular areas may be brought about; a matter in which of course the heart's action can exert no influence. You know how the regulation is effected; the means to this end are always the same, namely, *change of resistance in the arterial channels.* For it is clear, without further explanation, that the quantity of blood flowing into any vascular area must vary with the sum of the resistances in the arteries leading to it; the quantity of blood flowing into the vessels of the area in question will be less when the resistance is increased, and greater when the latter is diminished. In order to augment or reduce the resistance the organism has recourse to the expedient of *contracting or dilating the lumen.* Let us therefore take a brief survey of the forces capable of altering the size of the lumen of a vessel, and of the conditions under which they are normally called into action.

It must be noticed, in the first place, that the vessels are *elastic tubes;* they can therefore be stretched by strong internal pressure, and are able, on the other hand, to adapt t es to their contents when the quantity of blood con-
hem is diminished. The blood-pressure is naturally
cessful in effecting the stretching, the less the

elasticity of the vessel in question; thus it succeeds most readily in the veins, very easily, moreover, in the branches of the *a. pulmonalis*, as we saw already; nor does the elasticity of the arteries of the muscles and intestines appear considerable; and the same is known of the retinal vessels—they offer no great resistance to distending influences. On the other hand, the arteries of the skin, like all vessels possessed of a strongly elastic *tunica media*, are distensible only with difficulty, and for the same reason, *i. e.* owing to their greater elastic force, they adapt themselves the more rapidly to their diminished contents. It is on these grounds comprehensible that the retinal vessels should be fuller, and the volume of an extremity increased after peripheral irritation of the splanchnics, although the unaltered superficial temperature of the limb proves that the vessels of the skin have not dilated; the vessels supplying the muscles are more readily stretched by the increase of blood-pressure than are the cutaneous vessels, and take up the greater part of the blood which was dislodged from the vessels of the trunk by the irritation of the splanchnics.*

I have just intimated that the muscular portion of the vessel wall plays an essential part here. But its chief importance is manifested in an entirely different direction, inasmuch as it is pre-eminently the *degree of contraction of the circular muscular coat* that determines the size of the arterial lumen. The function of the *tunica media* is immediately under the control of certain centres—mechanisms having the characters of ganglia perhaps and situated in the wall of the vessel itself.† At least this view affords the simplest explanation of the tonic contraction which the arteries retain after division of the vaso-motors, or regain after a time although the divided nerves have not been restored: yet it must not be forgotten that vaso-motor nerves running in other trunks, whose action is ordinarily very feeble, may possibly under such circumstances accommodate themselves gradually to the greater demands upon them, and assume the tonic function of the chief constrictors after these have been thrown out of action.[*] Whether indeed the alterations in the state of contraction sustained by the vessel wall under the influence of some local agencies are to be ascribed to an effect on the nervous apparatus of the vessel wall or to one on the musculature itself, cannot so far be decided in any case. That heat and cold directly relax and excite the musculature, can be no more reasonably doubted than can the direct effect of electrical stimulation. But we are acquainted with reactions more difficult to interpret. Thus it has been shown in the laboratory of Ludwig, to whom we owe most of what we know of the life of the vessel wall, that the arteries of an organ which has been withdrawn from all nervous influence contract when blood overloaded with carbonic acid flows through them; sundry poisons produce the same effect when circulating with the blood, while others, such as atropine and chloral bring about a contrary condition, a relaxation. It is highly interesting, moreover, that the arteries contract against strong fluxion, and, on the other hand, relax on being for some time completely deprived of blood. In view of this manifold testimony to a spontaneous life in the vessel walls, it is not surprising that the state of contraction of their musculature should apparently be liable to *idiopathic* variations, *i. e.* that vessels cut off from the nervous system should show spontaneous changes in their lumen, whose rhythm is absolutely inconstant.[†]

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* Basch, 'Arbeiten des Leipz. physiolog. Instituts,' 1875, and 'Oesterreich. med. Jahrbücher,' 1876, Heft 4; Ostroumoff, 'Pflüg. A.,' xii, p. 219.

† Mosso, 'Leipz. Arb.,' 1874; C. Ludwig, 'Die Nerven der Blutgefässe,' Im neuen Reich. 1876, No. 1; Gergens und Werber, 'Pflüg. A.,' xiii, p. 44.

Neither have the mechanisms by whose agency the *nerves* supplying the vessels influence their calibre been so far determined; our acquaintance with the facts even is far from sufficient. True, it has long been known that in the majority of organs nerves exist, whose irritation is followed by a *constriction* of the arteries coursing through these organs; and the existence of *dilator nerves* in the tongue, the penis, the salivary glands, is equally beyond dispute. The nerves of the last category have acquired a practical interest since we—thanks chiefly to the labours of Goltz and Heidenhain[‡]

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[*] Stricker, 'Wien. med. Jahrbücher,' 1877, p. 415.

[†] Mosso, l. c.; C. Ludwig, l. c.; Gergens und Werber, l. c.

[‡] Goltz, 'Pflüg. A.,' ix, p. 174, xi, p. 52; Ostroumoff, ibid., xii, p. 219; denhain und Grützner, ibid., xvi, p. 1; Kendall und Luchsinger, ibid., p. 197.

—became conversant with the fact that, in the skin and muscles, a very considerable dilatation of the blood-vessels ensues on irritating certain nerves. The experiments in support of this conclusion are extremely interesting and plausible, nor is their interest at all lessened by the circumstance that the attempt to discover in the internal organs anything analogous to the dilator, or, as Heidenhain calls them, *inhibitory nerves*, has so far miscarried. It has not as yet been possible, however, despite the most painstaking efforts, to obtain even in the vessels of the skin a clear idea of the conditions under which the dilators come into action, so much so that the existence of nerves which on irritation dilate the arteries of the skin *alone* still continues to be called in question by some authors.* Under these circumstances, who would venture to decide whether the vaso-motor nerves act on ganglionic mechanisms in the vessel walls or directly on the muscular coat?

That in the different portions of the spinal cord centres exist, by which the vaso-motor nerves passing out beneath the region in question are controlled, can hardly at present be disputed;† but the constrictors, at any rate, have their chief centre in the medulla oblongata, a centre which is, as you know, in a condition of permanent tonic excitation. I formerly mentioned that this vaso-motor centre is strongly excited by dyspnœic blood; *anæmia*, whether general or localised in the medulla oblongata, has the same effect, which will be the more certainly exerted in proportion to the rapidity with which the amount of blood is diminished: the same result attends strychnia-poisoning. This centre is excited lastly by the irritation of centripetal fibres running in the nerves of sensation; concerning which fibres it is still undecided whether they are the sensory nerves themselves or specific fibres passing to the constrictor centre. On the other hand there is, as is well known, a centripetal nerve, whose stimulation inhibits the action of the vaso-constrictor nerves, namely, the *n. depressor*; yet it must be admitted that its influence may perhaps be referred to an excitation of the

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* Bernstein, 'Pflüg. A.,' xv, p. 575; Foster, 'Lehrb. d. Physiol., übers. v. Kleinenberg,' p. 185 ff.

† Cf. Luchsinger, 'Pflüg. A.,' xvi, p. 510.

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dilator centre. Heidenhain has proved that, in the vessels of the skin at least, their inhibitory nerves are reflexly excited by irritation of the depressor. Whether depressor influences on the innervation of the vessels are exerted by yet other centripetal nerves, either through inhibition of the constrictor or excitation of the dilator centre, we are unable to say at present; it is possible that such fibres may proceed from the peripheral vessels themselves to the central organ.* But one is not fully conscious how complicated are these relations, till the attention has been directed to single peripheral vessels. For it is self-evident that, on excitation of the vaso-constrictors concerned, whether of reflex or other origin, individual arteries contract quite independently of the condition of excitation of the centre, and that the same vessels can moreover dilate the moment their proper constrictors are thrown out of action or their inhibitory nerves irritated.

These are the forces, so far as we know them at present, that play a part here, and the conditions under which they become operative. By the interaction of these forces in various ways, those results are attained which are indispensable to the regular activity of all the organs, namely, on the one hand, the presence at the proper time of a sufficiently copious and powerful stream in the area requiring it, and on the other hand, the comparative emptiness of the blood-vessels in resting and inactive organs. Thus, what so frequently occurs in the natural sciences has happened here too; with our increasing knowledge an ever-increasing complication of relations has become manifest, so that the detailed analysis of the methods by which the organism in each individual case brings about, with the aid of the forces at its command, such a distribution of the blood as shall be adapted to the end it has in view, has grown to be one of the most attractive problems imaginable. In general it may be looked on as probable *that each organ regulates its own blood-supply*, but we are still very far from being able to specify in each instance the mode in which this regulation occurs. We know, indeed, that in some organs the stimulation of the same nerves that excite their function also dilates the arteries leading to them; thus it is with the salivary glands and with the muscles. But in many other organs, the digestive tract and kidneys, for example, an analogous connection has so far not been established; and it should therefore be taken into consideration whether the dilatation of their arteries during functional activity is not to be referred to factors other than the influence of the inhibitory nerves, *e. g.* in the kidneys to the amount of waste materials present in the blood. We are, if possible, still worse informed as to the influences securing that the contraction of the vessels shall always take place at the right moment; in many cases it is certainly a question of simple adaptation to the lessened contents by the elastic force of the vessel wall, as when the muscles or the brain become anæmic during digestion; but the possibility that at least just as frequently an active contraction co-operates must certainly be admitted. Be this as it may, you will not at any rate under-estimate the extent of the variations which the blood-supply of individual organs undergoes in a normal condition. According to Ranke,* the blood contained in the organs of locomotion in rabbits is almost doubled when the muscles pass from a state of rest into a tetanic condition; he estimates the blood-contents of the muscles of the rabbit at about 36·6 per cent. of the total amount in repose, and at as much as 66 per cent. in tetanus. The variations in the blood-contents of the intestine in the fasting state and during digestion are, if possible, still greater.

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* Latschenberger und Deahna, 'Pflüg. A.,' xii, p. 157.

Yet these conditions are not usually designated *anæmia* and *hyperæmia;* these names are applied, in a pathological sense at least, only when the deviations from the mean blood-contents of a part exceed the physiological limits, or when they present themselves in the absence of physiological causes; in any case consequently when the condition *persists for any considerable time.* It need hardly be pointed out that as long as the total quantity of blood is normal, the pathological anæmias and hyperæmias can only depend on changes of resistance in the vessels of the area affected. Imperfect action of the heart and changes of the total resistance in the vascular system will exert an influence on the distribution and flow of the blood throughout the entire body; *local alterations of the blood-contents* cannot be thus originated.

* Ranke, 'Die Blutvertheilung und der Thätigkeitswechsel der Organe,' 1871.

1. Local Anæmia.

The causes of pathological increase of resistance in the arteries.—Occlusion of the arteries.—Compensation by means of anastomoses.—Terminal arteries.—Results of narrowing of a terminal artery.—Results of its occlusion.—Engorgement.—Symptoms of anæmia.—Results to the vessel walls.—Hæmorrhagic infarct.—Results to the rest of the vascular system.—Proximal rise of pressure.—Compensation by decrease of resistance elsewhere.—Locality of this.

If we begin by considering the arteries, we find that a pathological increase of resistance may result in them: 1, *through immoderate enhancement of the natural resistances, i.e.* of the contraction of the circular muscular coat; and 2, *through the accession of new abnormal resistances.* The former may be the consequence of very low temperature; in a part of the body exposed to very intense cold the arteries undergo very considerable contraction at a temperature much higher than would be required to freeze the blood. A further means of producing strong contraction of the arteries of a part consists in the irritation of their vaso-constrictors. On passing a somewhat strong induction-current through the cervical sympathetic of a rabbit, the vessels of the ear contract instantaneously, and the same effect is produced on the intestinal vessels by stimulating the splanchnics. Irritation of the constrictors plays a part in pathology also. For there are vaso-motor *neuroses, i. e.* constrictions of morbid origin, appearing paroxysmally in the arteries of a part, *e. g.* of the hands, one half of the head, &c.; moreover, *neuralgias* are not infrequently accompanied by tonic contraction of the arteries in the area of distribution of the affected nerve; the contraction of the small arteries of the skin associated with the rigors of fever is also to be classed here; then, too, the vaso-motors are strongly excited by several poisons, *e.g.* opium. Lastly, paralysed parts are often observed to be anæmic and cool, which is attributable in part to the implication of the vaso-motor nerves in the morbid process, and in part, in the case at least of the arteries of the muscles, to the circumstance that, owing to the muscular inactivity, no more than a small amount of blood ever reaches the arteries, and the latter become gradually and permanently narrowed.

New abnormal resistances may make their appearance in the arteries either (1) *within the lumen itself*, or (2) *from without*. Amongst the internal varieties are to be cited, in the first place, morbid processes in the arterial wall, such as the sclerosis of the intima and the calcification of the muscularis already mentioned; by these the wall is thickened and the lumen narrowed, while at the same time the elasticity of the vessel is lessened and its distension by the pulse-wave essentially impeded or even rendered impossible. To the same class of processes belongs the endarteritic thickening of the intima, or *arteritis obliterans*, as C. Friedländer* calls it, a condition which has been regarded as specifically syphilitic, though incorrectly so in my opinion. In the next place, the deposition of clots on the walls of the veins, so-called parietal thrombi, must be considered; this process is not, however, confined to the veins, for sclerotic or atheromatous portions of the arterial wall are especially liable to become the seats of coagulation, so that both factors here combine to increase the resistance.

On the other hand, the agencies acting from outside the vessel which cause narrowing of a *limited* portion of an artery, are tumours, cicatricial strictures, and external constrictions. Or the external pressure may be applied not merely to one point of an arterial branch, but be distributed more generally, compressing an artery together with its branches, or even the capillaries fed by it as well, so as to involve the entire vascular supply of a part. This is the case in voluminous tumours and exudations, in collections of air or of liquid causing considerable distension of the walls of a cavity, or occupying a cavity whose walls are unyielding and incapable of distension; thus the vessels of the brain are compressed in severe hydrocephalus, those of the lung by a voluminous pleuritic exudation or by a pneumothorax with air-tension, those of the intestine in extreme meteorism.

The pathological hyperæmias of other organs must be mentioned as the third chief cause of local anæmia. This is a variety of local anæmia which may in itself attain very great importance; but its discussion will be advantageously postponed till after the hyperæmias have been considered, inasmuch as these constitute its primary determining factor.

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* C. Friedländer, 'Med. Ctrbl.,' 1871, p. 65; Heubner, 'Die luetische Erkrankung der Hirnarterien,' 1874; Baumgarten, 'Virch. A.,' lxxvi, p. 268.

The highest degree of increased resistance in an artery is brought about, as is self-evident, by its *occlusion*. That tetanic contraction of the circular muscular coat may produce this effect can at any moment be demonstrated by powerful electrical stimulation; but such occlusion will hardly ever be of moment in pathology, for both muscles and nerves will no doubt be speedily wearied, and thus the channels again become pervious. On the other hand, it is not uncommon for the lumen of an artery to be completely occluded by so-called "*obstructing plugs*," either thrombi or emboli; or the channel may be obliterated by excessive pressure and constriction applied from without, of which the simplest example is afforded by the *ligature*.

On more particularly examining into the consequences to the circulation through a part from an increase of resistance in its arteries, one point is found to be of critical importance for the whole process; namely, *the presence or absence in front of the seat of increased resistance, i. e.* between the obstacle and the capillaries fed by the artery in question, *of another arterial offset directly continuous with some free artery or other*, and forming, consequently, a true *collateral*, or more correctly, *anastomotic* branch. If such be present, the subsequent course of events is very simple. For the blood is conducted by means of the anastomosis into the section of the artery lying beyond the narrowing, and the circulation through the capillaries and veins previously fed by the affected artery now proceeds in a regular manner. In this case it is obviously immaterial whether the abnormal resistance in the artery be trifling or great, *i. e.* whether the vessel is merely narrowed or completely occluded; and it is also immaterial whether the anastomosis opens immediately beyond the obstacle in the occluded artery or whether other lateral branches pass off in the intervening space; for in the latter case these will also draw their blood from the anastomosis. The only point of importance here is the *relative size* of the occluded and the collateral arteries. For the larger the latter and the more abundant the quantity of blood supplied by it, the more readily and, in particular, rapidly will compensation take place; and to this end it will evidently be conducive, that the general arterial blood-pressure be high and the heart work vigorously. If, on the other hand, there be a pronounced disparity between the size of the artery whose blood-stream is impeded and the anastomosis, the latter cannot, at least at first, forward as much blood into the area of distribution of the artery concerned as should normally reach it; the action of the increased resistance is not removed, but merely weakened, and the consequence in this case too is *local anæmia,* though of a somewhat milder character.

Such compensation is wholly impossible when the obstacle is not seated in a circumscribed portion of the vessel, but involves the artery in a greater part of its extent beyond the point of inosculation, *i. e.* where it includes the anastomosis, or where the whole of the arterial branches together with the capillaries are implicated. It is also impossible when no anastomosis is present between the resistance in the artery and its capillary area, when consequently the obstacle is situated in a *terminal artery.* The first condition is found in anæmia dependent on vaso-motor influences; in what organ the latter may make its appearance depends altogether on the anatomical arrangement of its vessels: I remind you by way of illustration that the branches of the renal artery, as well as those supplying the spleen, do not anastomose after entering their respective organs.*

The direct consequences to the circulation of the affected part resulting from the increase of arterial resistance may in these cases be estimated without much difficulty, for the effect of the resistance on the blood-stream may be briefly formulated as follows: 1. *Every resistance interpolated at any point in the vascular system increases the tension in the proximal portion.* 2. *Every resistance renders the local equalisation of differences of pressure difficult,* i. e. *retards the stream.* The greater the resistance consequently at any point, the greater the pressure behind it, and the less the quantity of blood flowing in the unit of time, or the slower the blood-stream up to and beyond the impediment. Applied to increased resistance in the arteries, these considerations show in the first place that the arterial blood-pressure must be augmented proportionally to the amount of the resistance; but on this subject and on the different modes of compensation, more hereafter. We shall confine ourselves for the present to the vascular area in whose afferent vessels the resistance is increased, and, after all that has preceded, we may dismiss the topic in a few words: *the greater the resistance the less blood can flow into the vessels and the slower its forward motion through them.* This imperfect filling and slow stream will prevail up to the point where a stronger and ampler, if possible augmented, blood-stream unites with the weak one. But since the pressure in the neighbouring capillaries is inadequate to create a flow of normal vigour in the anæmic capillary area, the union will, in the absence of arterial anastomosis, take place only in the *veins;* the anastomoses form but a particular example of the general law. Accordingly the dimensions of the poorly filled vascular area depend altogether on the seat of the pathological resistance. If only a small terminal artery be narrowed, the anæmic area is proportionately limited, for then it is the arteries of the immediate vicinity that are hyperæmic, in a state of fluxion, so that one of these vessels, in which the blood flows with increased pressure and velocity, will soon discharge itself into the imperfectly filled vein. On the other hand, if you stimulate the cervical sympathetic in the rabbit, almost no blood flows from the exposed principal vein of the ear during the passage of the electric current through the nerves. You may observe the like effect in the *v. femoralis* of a dog whose sciatic is tetanized, and Basch saw the blood-stream in the portal vein almost dry up during the period of greatest excitation of the *n. splanchnici.*[*]

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* Cohnheim, 'Untersuchungen über die embolischen Processe,' Berlin, 1872.

But if we more closely examine the circulation in the anæmic vascular area certain differences become apparent which are conditioned essentially by the degree of the interpolated resistance. If the latter be moderate in amount, so that the blood in front flows under a tension which, though reduced below the normal standard, continues tolerably high, the sole result is more or less *retardation of the blood-stream.* Should, however, the resistance exceed a certain value, and the tension in front of it become minimal in consequence, a quantity of blood will then force its way from the capillaries bordering on and communicating with the anæmic region into the vessels of the latter. The amount of blood in the anæmic portion is thus increased; nevertheless the pressure under which the blood penetrates is, as already remarked, far from sufficient for the establishment of a proper flow. Rather the portion which has penetrated from the periphery resembles in its subsequent movement the original blood of the area in question, *i. e.* it passes very slowly forwards toward the veins. And the degree of forward motion may under such circumstances become so slight, *that it ceases to be sufficient to keep the specifically heavier blood-corpuscles suspended in the liquor sanguinis,* and allows them to settle in the capillaries. The consequence is obvious; a tolerably large quantity of red blood-corpuscles must gradually accumulate in the capillary vessels of a highly anæmic part. When the resistance is extreme, *i. e.* when an end artery is not merely narrowed but completely occluded, a fresh complication arises. For here the pressure in the vascular area in front of the occluded spot is equal to zero, so that no sort of motion can take place in it; the stand-still of the blood is complete, the vessels being more or less full in proportion to the rapidity with which the closure has taken place, *i. e.* according to whether the arteries have still been able to discharge their contents or not. But this area, from which tension is wholly absent, not only communicates peripherally with the adjacent capillaries but opens at some point or other freely and directly into a vein whose blood flows under slight but still positive pressure. The necessary consequence must be the establishment of a *retrograde* stream into the occluded area; this will be maintained till the latter has received so much blood from the vein and the capillaries of the neighbourhood that a state of equilibrium between the tensions in the anæmic area and communicating vein is established. This stream cannot from the nature of the case be more than a tardy one, so that the *retrograde filling* may be absent altogether or very inconsiderable should any other obstacle, such as gravity, for example, act in opposition to it. In particular, it can only take place, as will at once occur to you, when there is no obstruction from the presence of *valves* in the veins. But in an area whose veins are valveless the amount of blood penetrating laterally from the capillaries and in a retrograde manner from the veins may be so considerable that it will be proper to speak of actual *engorgement*; occasionally the entire part, whose afferent vessels are occluded, assumes a uniform intensely dark red appearance. The whole process of engorgement and retrograde flow may be followed most conveniently and clearly in the tongue of a curarised frog. The application of a ligature to one of the two large arteries coursing one on each border of the tongue from the lower surface of the buccal cavity, or, perhaps, in addition to any anastomoses connecting these two vessels, is all that is necessary to effect our purpose. The veins it is true are here provided with valves, but these are rudimentary and immovable, and do not therefore constitute any impediment to the retrograde flow of the blood.*

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[*] Basch, 'Arb. aus dem Leipz. physiolog. Institut,' 1875.

A diagnosis as to whether a part of the body is in a condition of *anæmia*, or *ischæmia*—to adopt the term proposed by Virchow—is, of course, not difficult if the affected organ is situated superficially, and therefore accessible to direct inspection and examination. An anæmic part will—if none of the complications just described is present—be *pale*; its temperature must very soon be reduced, and it will feel *cool* to the touch, simply because the amount of heat supplied to it no longer counterbalances the continuous loss of heat by radiation, after the quantity of blood entering the vessels of the area in question has diminished. Lastly, the *turgor*, which depends essentially on the adequate fulness of the vessels, will as a rule be less in an anæmic part. That a decrease in the juices of the parenchyma co-operates in producing this *flaccidity* cannot be asserted off hand, for though it is certain that transudation and lymph entirely cease to be formed in a portion of the body altogether deprived of blood, whose arterial blood-stream is completely shut off, it must not be forgotten, on the other hand, that recent [illegible] in

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* Cohnheim, l. c.; Kossuchin, Virch. A.,' [illegible]

Ludwig's laboratory have shown that the production of lymph is much more independent of the vigour of the flow through the arteries of a part than was formerly generally assumed.*

Moreover, it will appear self-evident to you that metabolism must be impaired in an anæmic organ, and that the *functions* as well as the *nutrition* of the organ must suffer in consequence, both of them in proportion to the severity and duration of the anæmia. It may be said in general that anæmia enfeebles or depresses the functional power of an organ, that it is gradually followed by emaciation or *atrophy*, and that, should the blood-supply fail completely, the affected part succumbs irrecoverably to *necrosis*, death. We shall again have to recur to these matters, and to deal with them thoroughly in connection with the pathology of metabolism and in our treatment of the individual organs; here we shall merely discuss briefly *the effects of anæmia on the vascular mechanism itself*, i. e. *on the heart and vessels.* We have already examined the consequences of anæmia to the heart itself. For increase of resistance in the coronaries is immediately concerned here, and you will feel perfectly at home on the subject, if you only recall what I formerly told you of the results that ensue after occlusion of the coronary arteries, on the one hand, and after sclerosis of the same vessels, on the other.

With regard to the vessels, I have already stated that they *dilate* when no blood has flown through them for a time. Yet if the blood has been excluded from the vessels, if anæmia in the fullest sense of the word has lasted longer than a brief period, something more than dilatation occurs. On firmly applying a ligature to the root of a rabbit's ear so that the entrance of blood into the vessels and into their *vasa vasorum* is rendered impossible, allowing it to remain in position from eight to ten hours, and then removing it, *the ear immediately commences to swell to a greater or less extent.* It displays a doughy tumefaction of a rosy hue, and on examining into the cause of the swelling you find the meshes of the tissues of the ear distended with fluid and moreover filled with a more or less large quantity of lymph-corpuscles. The longer the interval allowed to elapse before loosening the ligature the greater will be the quantity of lymph-corpuscles found in the meshes of the tissues; while if the ligature have remained applied for about twenty-four hours, you never fail to find dark red spots and streaks in the swollen ear, recognisable to the naked eye, but more clearly on microscopical examination, as punctiform and linear *hæmorrhages*. The size and number of these hæmorrhages are variable, yet it may be said in general that the effusion is abundant in proportion to the duration of the anæmia. Sometimes the ear is metamorphosed into a greatly swollen dark-red organ infiltrated through and through with blood. This, of course, has its limits. For when the ligature has been applied for fully two days and more, the ear commonly continues cold, shrunken, and dry, in which case it simply withers up without any other event being observed.*

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* [illegible] 'Arb. aus dem Leipz. physiolog. Inst.,' 1873; Emminghaus, [illegible]

What is the significance of this whole series of phenomena recurring with such perfect constancy in all organs after they have been robbed for a time of their blood-supply? Now, that the swelling of the ear and still more the hæmorrhagic infiltration must have had their starting-point in the vessels will not be doubted by anyone, and since the lymph-corpuscles are in no way distinguishable from colourless blood-corpuscles, it is *a priori* probable that they are also derived from the blood-vessels. On direct microscopic observation of the whole process in the tongue of the frog, this probability is converted into certainty. For there is not the least difficulty in here determining not only the occurrence of general dilatation on loosening the ligature applied for some hours; one may also convince oneself that, after the disappearance of an anæmia of some days' duration, *colourless and red blood-corpuscles, together with liquor sanguinis, pass in abundant*, indeed superabundant, *quantity, through the walls of veins and capillaries.* While reserving the more thorough study of these remarkable processes for a subsequent occasion, it follows from what has just been stated that *the function of the vessel walls* is intensely injured by an extreme anæmia. Blood-vessels through which and through whose *vasa vasorum* no blood has flown for a considerable time are no longer capable of confining the blood in their interior, but allow their contents to percolate through them in quite an abnormal manner; *the permeability of their walls, their porosity*, has therefore become abnormal. Moreover, this holds good, as I may at once remark here, of the capillaries and the veins alone, and not of the arteries; to the two former, however, it applies in all organs with only a single point of difference, namely, that the vessels of the different areas react with unequal vigour and rapidity to the ischæmia. Why it is that the vessels of the intestines and of the brain are so soon damaged by cutting off their blood-supply, while those of the skin and muscles are so slow to receive injury, still requires to be cleared up; the fact is but a new link in the chain of phenomena which points to the conclusion that the vessels of the various areas are far from altogether similar and equivalent in point of physiological and histological characters. Those of you who have already applied yourselves to the study of surgery do not require to be reminded how great an importance the capacity of the vessels of the skin and muscles to withstand anæmia has attained in modern surgical technique; for it was this that allowed Esmarch to venture on the application for hours at a time of an india-rubber tube to an extremity, in order that he might be able to operate bloodlessly.

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* Cohnheim, 'Untersuchungen über die embolischen Processe,' Berlin, 1872.

On viewing in the light of these experiences the peculiar case already discussed, namely, the occlusion of a terminal artery, we find it to be a necessary consequence that after a time, when the walls of the capillaries and veins have become abnormally permeable as a result of the failure in the arterial blood-supply, the blood that has forced its way into them must pass through their walls and infiltrate the meshes of the tissues of the neighbourhood. Under these circumstances the part in question becomes filled to distension with blood, which occupies not merely the vessels but also the space surrounding them; the meshes of the tissues of the part come to be completely stuffed with blood, there arises what is commonly designated a *hæmorrhagic infarct*. This, you perceive, is the combined effect of the engorgement and of the abnormal permeability of the capillaries and venous walls brought about by the arterial ischæmia; where either of these factors is absent there can be no true hæmorrhagic infarct.

You will bear in mind, however, that the alterations in the vessels just described are produced by the absence of blood or by very extreme anæmia only. We shall not expect so intense an action from simple increase of resistance of trifling amount, *i. e.* from ordinary anæmias. In fact we frequently see a paralysed extremity in a condition of marked and persistent anæmia for months together without any appearance of swelling or hæmorrhage. Nevertheless you must not rely too much on a scanty blood-stream to maintain the vessels intact; for it is nothing rare in the experience of the surgeon for an extremity to swell slightly for some days, to become *œdematous*, after ligature of its principal artery. Yet here a quantity of blood, although at first much reduced, certainly reaches all the vessels of the extremity from the collaterals entering them—the same collaterals by whose gradual dilatation a regular circulation is at last re-established—nor has blood ever ceased to reach them from the moment of application of the ligature, so that the complete absence of blood at any time is altogether out of the question. A kidney is not altogether deprived of its supply of blood by ligature of the *a. renalis*; for a small quantity continues to reach the vessels of the organ from those of the capsule and ureter. Nevertheless, after ligature of the *a. renalis* in the rabbit it is very common to find hæmorrhages especially in the medullary but also in the cortical portion; indeed, true hæmorrhagic infarction takes places place here, the blood being supplied, as Litten* has shown, either not at all or in very trifling quantity by the retrograde flow from the *v. renalis*, and practically by the collaterals already mentioned.

After having till now devoted ourselves to the minute study of the circulation in the anæmic region itself, it will be proper to discharge the second part of our task and to examine *into the condition of the remainder of the vascular system* when a local increase of resistance has occurred anywhere in an artery. With regard to this subject the question is presented in its simplest form, where the local anæmia follows secondarily on a local hyperæmia; since in this case we have not to seek far in order to discover where the blood that has left the anæmic area is hidden; for it is absent only because the hyperæmic area contains a suberabundant quantity. On the other hand, the question as to the abode of the blood in primary local anæmia is by no means so easily answered as was formerly supposed; for the whole complicated mechanism recently described, by means of which the body is enabled to regulate the resistance in the various portions of the vascular system, comes into play here.

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* Litten, 'Zeitschr. f. klin. Med.,' i, Heft i.

The first and immediate result of an elevation of arterial resistance is, I need hardly repeat, *a rise of arterial pressure on the proximal side.* You will understand me to speak of the *general* arterial pressure; for to suppose that the tensions in the various arteries of the body can ever, amongst themselves, present differences other than such as may be conditioned by the remoteness of the respective vessels from the heart would be to misunderstand the fundamental laws of hæmo-dynamics. On connecting a manometer with the *a. femoralis* by means of a ⊢ shaped cannula, it is the lateral pressure in this vessel you measure; on now occluding the peripheral portion of the femoral in front of the cannula you measure, it is obvious, the lateral pressure at the point where the femoral arises, in this case, therefore, that of the *iliaca externa* or at most of the *iliaca communis;* and this pressure is precisely the same as that of the other iliac whose femoral offset is pervious. And if, instead of simply occluding the femoral, you encircle the upper part of the thigh of a dog with an india-rubber tube, so as to completely prevent the access of blood to the extremity, a manometer placed in the femoral immediately above the constriction shows a rise of pressure not a whit higher than that exhibited by a second manometer in connection with the animal's carotid. Precisely the same results are observed in both the manometers, if, instead of ligaturing an entire extremity, the sciatic be divided, and a strong induction-current passed through the peripheral portion. *The general arterial blood-pressure rises in proportion to the amount of the resistance, and this rise is maintained till compensation is effected by the decrease of the resistance elsewhere.*

But where and how does this decrease take place? Were the elasticity the only source of resistance in the arteries, everything would be very simple; the increased pressure would go on distending the still pervious vessels till the united sectional area of the effluents became exactly as large as it was before the narrowing of one or more of them. This actually occurs in the lung, as we have already shown (p. 105); should a number of pulmonary arterial branches be occluded by any pathological process, the remainder all undergo, in consequence of the increase of pressure, a uniform dilatation, so extensive that during the same interval there now flows through the reduced vascular system the same quantity of blood as before. Such a uniform stretching is utterly out of the question in the systemic circulation, simply because, as already stated, the elasticity of the different vascular areas is very unequal; the vessels of the muscles can more readily relax under the influence of the increase in lateral pressure than can those of the skin. Add to this, however, the capacity inherent in the arteries, of the skin for example, and also of the kidneys to contract actively against an increased rush of blood; and consider above all the power possessed at all times by the nervous system of neutralising the effect of the augmentation of lateral pressure by strengthening the contraction of the circular muscular coat, or, on the other hand, of co-operating by causing the relaxation of these fibres. Thus the nature of the regulation in these cases is in truth unusually varied, and it is absolutely untrue that precisely that vessel is dilated which arises from the aorta close above the occluded one—an idea which in the abstract is very apt to occur to one's mind. Rather the blood dislodged from the anæmic area goes wherever it finds the resistance least, and it finds this, at any rate lastingly, *wherever it is itself most needed.* I do not deny that this whole view sounds very teleological, yet you will not allow yourselves to be misled by this as soon as you perceive that the law just enunciated is merely a brief expression of the facts of the case.

Let us review with this object all the possible individual cases. It very frequently happens that in a part of the body receiving its blood from several arteries one or more of these undergo an increase of resistance; or that in an organ, all of whose parts are appropriated to the same function, one of them is deprived of blood. The latter occurs, for example, when a branch of the renal artery is occluded, or when through some accident or other a coil of intestine becomes anæmic; the simplest example of the first is ligature of the *a. femoralis* in the hinder extremity, or of one of the carotids in the head. What takes place here? After the occlusion of the affected channel the blood, unable any longer to enter it, passes *into the remaining still pervious arteries* leading into the part of the body in question. These are, it is true, in part collaterals; so it is in the head, the extremities, and the intestines: in the kidney, however, the branches of the *a. renalis* have, as I formerly intimated, no connection the one with the other; moreover, in the intestines the loops bordering on the anæmic one become hyperæmic, when the occlusion of the arteries of the anæmic loop has been produced in their whole extent by injecting chromate of lead in suspension, and a collateral circulation thus rendered impossible. That, furthermore, the respective positions of the arteries concerned, *i.e.* the order of origin from the main trunk, is perfectly immaterial, is best shown by the example of the carotid already adduced; for a hyperæmia of the right arm has never been observed after ligature of the *carotis communis dextra,* although in man, as you know, the right carotid and right subclavian spring from the same trunk, the *anonyma.* It is the *carotis communis sinistra* arising later from the aorta and to a less extent the vertebral, an offset it is true of the subclavian, which now carry to the head the whole of the blood whose passage through the carotid is barred. In the dog and the rabbit, however, you may occlude the *vertebralis* and *carotis dextra,* and even the *carotis sinistra* as well, and yet the head still receives almost the same quantity of blood as before, because it is the left subclavian and not the right that dilates, and this dilatation, far from taking place in all its branches, *occurs only and solely in the vertebral.*

The rule is still more clearly exemplified, when one of two organs having the same function but lying apart from each other becomes anæmic. *After ligature of one arteria renalis* *its blood passes into the other vessel and nowhere else.* T hypertrophy which so quickly ensues in one kidney on loss of its fellow was long since suggestive of this. T experiments of Rosenstein, however, afforded the first str proofs of the fact; in dogs which had borne well the ope tion of ligaturing one of the renal arteries or—what for purpose is fully equivalent—the extirpation of a kidn he observed no sort of alteration in the amount or consti tion of the urine; neither the water- nor the urea-conte were in any way changed.* Notice that this takes pl whether the right or the left renal artery is occluded, wh only in the case of the left could it be supposed that other artery dilates because it is the nearest vessel arisi from the aorta on the proximal side. That the same thi occurs in other paired organs or in such as have analog functions is in my opinion clearly supported by the occurre of hypertrophy in the remaining organs after the destruct of some of them; for how could one testicle grow after moval of the other, or how could the lymphatic glands large after extirpation of the spleen, if they did not rece a larger quantity of blood than normal?

But what happens when anæmia arises in an organ wh performs its functions in a completely isolated and indep dent manner, and which, therefore, cannot be replaced another? The aforesaid rule appears to leave us complet in the lurch here, for in anæmia of the intestines or in obstr tion to the entire arterial blood-supply of an extremity, can say where the blood is most needed? Which org should by their excessive action compensate for the redu action of the intestine or the extremity? Basch, as I m tioned already, has actually observed an increase in the volu of the extremities, and at the same time a greater fulness the retinal vessels of the dog on irritating the splanchn and it is, conversely, not improbable that the vessels of abdomen become hyperæmic on sudden occlusion of vascular channels of one or more extremities; at least a tightly binding the hind leg of a dog with an elastic band the quantity of blood in the other hind extremity does increase to such an extent as to give rise to any observa elevation of blood-pressure in its principal vein. But even did the blood cut off from the left leg enter the right one this would obviously be no confirmation of our law, since one leg cannot by any means do the work of both.

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* Rosenstein, 'Virch. A.,' liii, p. 141.

But this location of the blood elsewhere is only, if I may say so, an expedient in time of need, and in any case of a *temporary* character. If the constriction of the vessels of the intestines or of the extremity arises suddenly, the displaced blood enters the dilated channels only to return, on the abatement of the constriction, into the old paths; after every interruption in the irritation of the splanchnics Basch observed a decrease in the volume of the limb. But that an hyperæmia of the extremities in anæmia of the intestinal vessels, or of the vessels of the abdomen during increase of the arterial resistance in the limbs should be a *lasting* condition, would be an utter contradiction in the economy of the organism, which never supplies more blood to a part than suffices for its immediate wants. Severe intestinal anæmia of a permanent character can hardly occur in pathology, since life is scarcely compatible with the consecutive atrophy of the intestine. It is, however, certainly compatible with stunting of the extremities, indeed with their complete absence. Yet in persons one or more of whose limbs have been amputated without the loss of more than a trifling amount of of blood, there has never been observed any sign whatever of lasting hyperæmia of the abdominal viscera or of any other organ; neither does any hypertrophy of the thigh take place after removal of the leg, nor the stump betray in any respect the presence of an increased quantity of blood.

But there is nothing enigmatical in all this if you bear in mind that the organism does not keep a larger stock of blood on hand than is absolutely necessary to the nutrition of the organs and to the performance of their functions. As soon as an apparatus becomes stunted or perishes, and there is no longer any need for the blood formerly required for its work, a certain quantity has become an *overplus* in the body, and the same thing happens as ensues when the amount of blood present in an uninjured organism has been artificially increased; *the surplus blood is consumed* and removed, and no more blood than is required for the continued existence and function of the remaining apparatus is henceforward produced. It is possible in this way, you perceive, to avoid a permanent increase of blood-pressure and a lasting hyperæmia in any of the organs, although the capacity of the vascular system has been permanently diminished.

You see how fully justified I was in expressing the opinion that in local ischæmia the dislodged blood goes where it is most needed. Where the resistance in some of the arteries supplying an organ is increased, more blood enters the remaining pervious ones; in anæmia of a paired organ its fellow or another of like function obtains more blood; and should a function of the organism become impaired, or cease altogether, owing to a deficiency in the local blood-supply, the blood formerly appropriated to this end is no longer "needed," and is therefore completely removed and disappears. That the latter takes place by means of an increased gaseous and liquid excretion from the organism need hardly be mentioned expressly. On the other hand, our knowledge is far from adequate to a detailed explanation as to which of the expedients at the command of the body is employed to effect in any given case a decrease of resistance in precisely those arteries whose dilatation is desired. As far as collaterals are concerned, the idea at once suggests itself that it is the *paralysis* of the vessels of the anæmic area resulting from the anæmia itself that brings about a more plentiful entrance of blood from the anastomosing arteries; in particular, it harmonises very well with this hypothesis that a certain time must elapse before the collateral flow is properly established. Moreover, the latter is an experience that also applies to compensation brought about otherwise than by means of a collateral circulation, so much so that it is thereby to a certain extent rendered improbable that the dilatation of the arteries concerned is effected by the ordinary vaso-motor or vaso-dilator nerves. On occluding in the dog the *a. renalis* of one side, a corresponding increase in the blood-supply of the other kidney is far from taking place at once;* the operation has at first not the slightest influence on its blood-contents. Only slowly and gradually, and in dependence doubtless on the successively increasing accumulation in the blood of salts, urea, and of the other urinary constituents, is there established that augmentation of the blood-contents, that hyperæmia of the second pervious kidney, to which the Rosenstein experiment and the hypertrophy of one kidney after the permanent destruction of the circulation of the other bear testimony. This illustration may suffice to convince you that principles which shall hold good for every case cannot be laid down here, and that an analysis of the separate problems must be undertaken in order that the mechanism may be established by which the fulfilment of the desideratum, if I may use the expression, is attained. The localisation of the secondary hyperæmia being thus intimately connected with the function of the part concerned, it is obvious that many of the hyperæmias which have been referred to the class *collateral*, *e. g.* the red areola surrounding an abscess, cannot be such in our sense of the word, *i. e. secondarily conditioned by ischæmia;* they must be interpreted in quite another way, and are nothing more or less than *inflammatory* hyperæmias. And it follows, furthermore, that the exposition you have just listened to is not open to objection on the ground that a permanent hyperæmia of one kidney following extirpation of the other is incompatible with the general principle of the circulation in animals, in accordance with which no organ permanently receives a larger supply of blood than is indispensably necessary to the maintenance of its function. I remind you, in addition, of a fact on which I have repeatedly laid stress, namely, that the kidney, or testicle, or lymphatic gland whose supply of blood is permanently increased, *hypertrophies.* To the hypertrophied organ the increased quantity of blood is not relatively larger than is the normal amount to the organ of normal size. In the more voluminous kidney with its so much more numerous vessels, the arterial stream is just sufficient to fill a number of them strongly, while others must remain for the time being relatively empty; hence the fundamental law of the varying fulness of the arteries is maintained here also.*

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* According to experiments not yet published, which I carried out in conjunction with Ch. S. Roy.

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* The foundation of the physiology of all the local circulatory disturb-

2. Active Hyperæmia.

Causes of decrease in the arterial resistance.—Their brief duration.—Consequences to the circulation as a whole.—Consequences to the blood-stream in the congested area.—Symptoms of fluxion.—Influence on the lymph-stream.—Consequences to the heart and vessels.

Impossibility of local congestions of the lungs.—Hyperæmia due to falling off in atmospheric pressure.

As compared with the subject of increased resistance, which has occupied our attention so long, the problem presented by the alterations in the local flow and distribution of the blood which depend on *diminished arterial resistance* is much less complicated. For outside influences cannot assert themselves here, and we have in all cases to deal only and solely with a *falling off in the physiological resistance* more or less great, essentially therefore with a reduction in the tonic contraction of the circular muscular coat. Nor need I point out that an actual decrease of resistance is presented only when the dilatation of the artery in question extends as far as its termination in the arterial capillaries; local circumscribed dilatations of an artery, whether produced by abatement of tone at the spot affected, or, like aneurysms, by actual changes of texture, can never have the effect of diminishing the resistance, since immediately in front of them the lumen of the artery is again narrow. The sole consequence of an aneurysmal dilatation in a branch artery will be merely a greater or less retardation of the blood-stream within the compass of the dilatation, for the bed of the stream is broadened without any change in the accelerating forces.

One principal category of the true hyperæmias depending on diminished arterial resistance is already known to

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ances is Volkmann's 'Hämodynamik,' 1850, and the 'Arbeiten' of Ludwig's laboratory. Cf. besides the physiologies of Ludwig, Donders, Brücke, &c., Virchow, 'Handbuch der speciellen Pathologie,' 1854, Bd. i, p. 122; C. O. Weber in Pitha-Billroth's 'Handbuch der Chirurgie,' Bd. i, p. 62; Uhle und Wagner, 'Handbuch der allgemeinen Pathologie,' 7 Auflage, 1876, p. 231.

you, namely, the *collateral hyperæmia* supervening on local ischæmia. We have minutely considered what areas become hyperæmic when the blood is deficient elsewhere; we have also spoken of the means by which the compensatory dilatation of the arterial channels is effected; and you will look upon it as self-evident that the intensity and extent of the collateral hyperæmia should be all the more considerable, the more severe the primary anæmia and the larger the district over which it prevails. You will consequently feel a warmer interest in the second category of these hyperæmias, namely, the independent, or, if I may use the term, *idiopathic* variety, in which the abnormal cause acts by directly diminishing the resistance in an arterial channel. For the causes productive of a pathological diminution of resistance must be abnormal, although they cannot, it is true, produce this effect except by making use of the means normally employed by the organism to increase the blood-contents of a part, *i. e.* by direct relaxation of the vessel wall; this relaxation being brought about either by acting on the musculature itself or on its nervous arrangements, or by depressing the excitation of the vaso-motors or exalting the excitation of the dilators.

A degree of heat only a little above the normal temperature of the body directly relaxes, as every one knows, the musculature of the arteries. On placing the hand in hot water it becomes red, and the ear of a rabbit, after being immersed in a water-bath at 45°—48° very soon displays a really enormous dilatation and injection of all its vessels. In this particular case it is easy to demonstrate that the result is due solely to direct relaxation of the muscular coat; you need only ligature firmly the root of the ear and then expose it for some minutes to the action of the warm water; if, immediately on removing the ear from the water, you loosen the ligature, the same enormous dilatation of all the visible vessels makes its appearance just as before, reaching a higher pitch than it would ever in itself attain after such brief constriction. Another variety of dilatation, also dependent on direct muscular paralysis, will be readily understood in the light of the foregoing; it occurs in arteries on the sudden removal of great external pressure to which they have long been exposed and thereby compressed; thus the extirpation of a large tumour from the abdominal cavity or the rapid removal of a large ascites may be followed by an intense hyperæmia of the intestinal vessels, and the puncture of a large hydrocele by a hyperæmia of the vessels of the tunica vaginalis. Then, too, the dilatation appearing in the arteries of a part on mechanical irritation, for instance after rubbing vigorously a few times, must certainly be referred to direct relaxation, to atony of the circular muscular coat, which appears to be extremely sensitive to all sorts of external influences. Since we have learned from Mosso that certain poisons, such as atropine and hydrate of chloral, directly paralyse the musculature of the arteries,* we may be allowed the conjecture that the noxæ which cause the so-called acute exanthemata exercise amongst other effects a direct paralysing action on the arteries of the skin. Nevertheless these cutaneous hyperæmias border so closely on the province of inflammation that it appears advisable to postpone their discussion till we come to deal with the latter subject.

The second factor dilating the vessels, *paralysis of the vaso-motors*, plays a part in many other pathological hyperæmias. Wounds of nerves in which vaso-motor fibres run, or tumours that press forcibly on such nerves, must, it is evident, produce a hyperæmia by causing a falling-off in arterial tone. I formerly mentioned that solutions of continuity and foci of disease in the spinal cord destroy arterial tone in those parts of the body whose vaso-motor nerves leave the cord beneath the point at which its conductivity is interrupted. I believe I also laid stress on the fact that only those interruptions that are situated below the origin of the splanchnics are actually followed by *local* hyperæmias, while those situated farther up are always associated with lowering of the total resistance. Moreover, should the interruption of conduction concern only one half of the cord, the hyperæmia will obviously be confined to one side. Whether, however, a series of independent hyperæmias occurring paroxysmally as pronounced *neuroses*, and partly accompanied, partly unaccompanied by morbid irritation of sensory nerves, so-called *neuralgias*;—to decide, I say, whether these are to be attributed to direct or to reflex inhibition of the vaso-motor, or to stimulation of the dilator nerves, is impossible in the present imperfect state of our knowledge; we can merely say of them that they are hyperæmias depending on decrease of arterial resistance of nervous origin.

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* Mosso, 'Arbt. d. Lpzg. phys. Inst.,' 1874.

On surveying more carefully the various conditions, in which a morbid arterial hyperæmia can arise, an essential difference as compared with the anæmias cannot possibly escape you, namely, that practically no pathological process exists by which the arterial resistance is *permanently* depressed. The collateral hyperæmias form an exception; yet we were able to show in their case, too, that where congestion is lasting hypertrophy of the organ concerned is developed, whereupon the previous hyperæmia ceases to be such. But disregarding collateral hyperæmia, which is only a secondary condition, it is apparent, on the one hand, that the influences that decrease arterial tone are most of them of a more or less transitory character, and, on the other hand, please remember that even the division of the sympathetic does not cause permanent hyperæmia of the ear, but that after a time the arteries reassume their normal diameter. The dilatation, also, which ensues on the removal of severe compression, does not last long, for the re-establishment of a plentiful stream of blood into and through the vessels is the surest means of restoring the paralysed arterial musculature, exhausted as it is by long anæmia, so that here, too, the vessels gradually regain their normal calibre. The same is taught by the observation of other varieties of direct paralysis of the vascular wall, *e. g.* that following the action of poisons, provided only the dose of the poison be not overlarge, and the simple relaxation do not gradually pass into dissolution, death.

But whether the decrease of resistance be of long or short duration, the circulation of the part concerned will always, while the condition lasts, present definite deviations from the normal. For *a larger amount of blood must necessarily enter a part when its arteries of supply are dilated* than when they are not dilated. Whence does the blood come? You know already; *it is withdrawn from other arterial channels.* And this occurs not merely in the collateral hyperæmias, where of course the "withdrawal" is the primary determining event, but also in the remaining varieties; which, in contrast to the former, we have designated "independent." If we inquire, however, from which arteries the blood is on each occasion withdrawn, the answer will in a measure apply here too; *it leaves the part where it is least needed.* This is certainly the case when a portion of a large organ, each part of which is devoted to the same function, becomes hyperæmic; when a loop of intestine is more strongly filled than before, the neighbouring loops undoubtedly become emptier, and, on producing intense reddening and swelling of part of the spleen by dividing a number of its nerves, the remainder of the organ to which the uninjured nerves are distributed becomes proportionately pale bluish and shrunken. The right kidney certainly becomes paler when an excessive amount of blood enters the left. Where, however, the source of compensation is not as in these cases to a certain extent prescribed, *e. g.* in overfilling of a whole extremity or of the entire abdominal cavity with blood, remotely situated and extraneous vascular areas must contribute from their supply. In such cases it is especially the vessels of the muscles and intestines that constitute the reservoir from which the blood is ordinarily withdrawn, yet the syncope frequently observed to ensue on the application of the cupping-boot indicates that the vessels of the brain are sometimes called upon to cover the dilatation of the arteries of an extremity. Since, then, considerable functional disturbance may be occasioned by this proceeding, even when only once resorted to and then for but a short time, derangements of function would be unavoidable, and indeed of great moment were the compensatory anæmia to continue for a period or even to become persistent. It is for this reason important that, as just stated, idiopathic arterial hyperæmia is always of a transitory nature, for the secondary anæmia is consequently always brief, since it naturally gives place to the normal vascular fulness as the hyperæmia disappears.

But the collateral anæmias in all these processes are of great importance in another respect, inasmuch as it is by their agency that the arterial pressure is maintained at its normal elevation. Every decrease of resistance in the arterial channels would, in the absence of a contemporaneous rise of resistance elsewhere, lower the blood-pressure, and this in proportion to the extent of the region in which the resistance had been lowered or perhaps abrogated. If the vascular area is very large, if, *e. g.* the whole of the abdominal vessels are dilated after division of the splanchnics, the blood-pressure, as we were able to determine, falls to such an extent that an adequate compensation by constriction of the vessels elsewhere is impossible. The necessary consequence of section of the splanchnics is therefore a general retardation of the circulation, not only through the remainder of the body, but also in the area of the splanchnics themselves, in which now an abnormally abundant supply of blood flows sluggishly forward; and despite the hyperæmia less blood reaches the *v. cava inferior* and heart from the abdominal vessels than formerly when the bed of the stream was narrower.

The case is reversed, when the area in which the arterial resistance is relaxed is not so extensive as to render impossible the maintenance of equilibrium by a simultaneous rise of resistance in other places. For the arterial pressure, and consequently the difference of pressure in arteries and veins, now continues unchanged; the equalization of pressure, however, naturally takes place most rapidly where the resistance is least, *i. e. in the area whose arteries are dilated.* Hence it follows that not merely does a larger quantity of blood flow through the hyperæmic vascular area, but *the rate at which it flows is increased.* In this way a very powerful and rapid blood-stream will circulate through the part in question as long as the dilatation of the arteries lasts. If you watch the ear of a rabbit after division of the cervical sympathetic of the same side, you will perceive a multitude of small vessels which were formerly invisible, and which are quite imperceptible in the other ear; again, if you place your finger between the toes of a dog after having divided the sciatic in the corresponding leg, you feel a strong pulsatile beat in arteries that were previously hardly discoverable by the examining finger. The blood-stream now hurries through the capillaries much more rapidly than before, and a considerably larger quantity of blood enters the veins in the unit of time. On comparing the amount of blood flowing from the divided principal vein of the rabbit's ear, before and after division of the sympathetic, a really astonishing difference is sometimes revealed; formerly every five minutes a drop, and now that the arteries are dilated four or five every second. The great importance of the arterial resistance to the entire circulation through the capillaries and veins cannot be more intelligibly demonstrated than in these same hyperæmias. On connecting the *vena femoralis* of a dog with a soda-manometer by means of a ⊢ shaped cannula and then dividing the sciatic, you will at once see the venous pressure rise to double or three times its former height or even still higher. Even the rhythmical acceleration, the *pulse-wave* may under these circumstances be propagated through the capillaries into the veins, as was long ago shown by Bernard to be the case with the veins of the salivary glands on irritation of their vaso-motor nerves. That blood flowing with such rapidity has no time to become disarterialised but must retain its perfectly bright red colour on its arrival in the veins, will be clear to you without further explanation. But the venous stream, thus accelerated and strengthened, will preserve these characters as far as the confluence of others which, receiving their blood from non-hyperæmic parts, are poorly filled in comparison; in which connection I need hardly explicitly state that the compensation in the venous stream will be most favorable when the hyperæmic vein unites with the collateral anæmic one.

The signs of arterial or, as it is also called, *atonic*, *active* hyperæmia, hyperæmia of *relaxation*, and for which moreover the expressions *congestion*, *fluxion*, *determination* are also in use, are of course the very reverse of those of ischæmia. A congested part is brightly *reddened*; it is at the same time, at least if it be superficially situated, *warmer* than normal, since the amount of heat conveyed to it by the increased supply of arterial blood exceeds its losses by radiation; and its *turgor is greater* than normal simply because its vessels are all of them more strongly filled. As to whether an increased formation of lymph participates in the production of this turgor, a definite opinion cannot, so far as I see, be offered at present. After this had formerly on *a priori* grounds passed as an indisputable truth, it was shown by Paschutin and Emminghaus in Ludwig's laboratory that division of the sciatic in the dog has no influence on the amount or on the chemical composition of the lymph flowing from a cannula introduced into a lymphatic of the leg.* Yet, although this fact is easy of confirmation, and though it may moreover be determined with certainty that no alteration is experienced by the lymph-stream in the cervical trunk as the result of division of the cervical sympathetic, a certain reserve should be maintained before we proclaim that the formation of lymph is entirely independent of the state of fulness of the arteries. There is one place at least in which *the influence of the vaso-dilators on the production of lymph may be most strikingly demonstrated.* If in a dog the peripheral end of the divided lingual nerve be stimulated for some time by induction-currents of gradually increasing strength, a marked *œdema* supervenes on the enormous hyperæmia which rapidly sets in in the affected half of the tongue; this œdema is recognisable to the naked eye about ten minutes after the commencement of the stimulation, and continues to increase during the next ten minutes till it attains very considerable proportions. This very remarkable experiment, my acquaintance with which I owe to the kindness of Mr. Ostroumoff, is well calculated to excite doubt as to whether all congestions, no matter what their origin, are equivalent so far as the production of lymph is concerned; all the more so because some isolated facts in human pathology, such as the rapid formation of wheals in urticaria under the action of influences undoubtedly nervous, clearly point to an intimate relationship between lymph production and vascular innervation.

When dealing with the subject of collateral hyperæmia, I laid stress on the fact that a frequently recurring or a permanent arterial fluxion produces *hypertrophy* of the part concerned; the full consideration of the influence of congestion on the metabolism and function of the individual organs will be reserved for a future occasion. Here we need only discuss its consequences to the heart and vessels. Yet our knowledge of the conditions under which morbid congestion of the coronary arteries makes its appearance is too scanty to permit of a precise definition of its action on the function of the heart. True, it is probable that here too the frequent recurrence of congestion of the coronaries causes the heart to hypertrophy; at least we have every reason to look on physiological hyperæmia as the ultimate cause of an increase of volume of the heart in all cases where this is the result of increased demands on its work.

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* Paschutin, 'Arbt. d. Lpzg. phys. Inst.,' 1873; Emminghaus, ibid., 1874.

It is commonly held, even by physicians, that the vessels may readily rupture in consequence of strong congestion, and a more or less copious hæmorrhage be thus induced. Yet it would be a poor testimony to the excellence of our organisation were the vessels not even able to sustain such a moderate rise of internal pressure. This apprehension is moreover groundless; by suspending respiration in the dog you may raise the blood-pressure to an enormous extent, while at the same time, as Heidenhain has shown, the cutaneous vessels of the extremities are dilated;* nevertheless not the least trace of hæmorrhage will be observed anywhere, not even a single capillary bursts. At most it may occasionally happen in such extreme rise of blood-pressure that isolated ruptures are met with, occurring in those parts of the body where the capillaries are practically unsupported by the surrounding tissues, as in the retina, the brain, and also the conjunctiva. It is of course obvious that the vessels must be healthy, if their power of resistance is to stand so severe a test. When the capillaries are very delicate and susceptible of injury, as is always the case where they are newly formed, every moderately strong congestion is dangerous to the continuity of their walls; even arteries may rupture as the result of fluxion when their coats have become brittle through atheromatous disease or a similar affection.

On the contrary, healthy vessels are wont to become *thicker* and *more voluminous* under the influence of frequent or permanent congestion. The collateral hyperæmias afford the best illustration of this fact; for here it is not at all unusual for small vessels to develop gradually into really thick-walled and strong arteries. The intrinsic cause of this is undoubtedly to be sought in a lasting hyperæmia of the *vasa vasorum*, so that the phenomenon is the full equivalent of that hypertrophy of all the other organs which results from a sustained increase in fulness of the nutrient vessels. Whether, on the other hand, thickening and sclerotic processes in the intima of arteries may also be referred to arterial hyperæmia is, in my opinion, a question not yet ripe for decision; in any case the responsibility should then be thrown on the increased lateral pressure in front of a decrease of resistance rather than on the more vigorous flow through the *vasa vasorum*.

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* Ostroumoff, 'Pflüg. Arch.,' xii, p. 219.

Before dismissing the subject of active hyperæmia, permit me to allude to a not unimportant circumstance, as it seems to me, directly involved in what has already been stated. If, as we have seen, local hyperæmia can never arise, except through diminution of the resistance in the arteries concerned, it logically follows, since the branches of the *a. pulmonalis* have no tonus worth mentioning, that *a local arterial fluxion cannot exist in the lungs.* With regard to collateral hyperæmia, we were formerly able to show that it affects impartially the whole of the still pervious arterial channels. But it is obvious too that the hyperæmias which are called forth by the inhalation of hot steam or of gases that dilate the vessels will act, not on single branches, but on all the vascular ramification in the lung together. You see, the contrast to the systemic circulation is sufficiently striking.

Some of you may perhaps be surprised that I have not included *falling-off in atmospheric pressure* among the factors causing diminution of arterial resistance; this, however, is a peculiar case. It is certainly quite true that the arteries dilate under the action of the cupping-glass or of the cupping-boot of Junod; not only so, but the dilatation is never confined to the arteries alone, the veins, and even the capillaries being involved to an extreme degree. Nevertheless, the derangement of circulation so evoked differs *toto cœlo* from the congestive hyperæmia. For the partial vacuum must necessarily exert its *exhaustive action* in *all* directions, so that blood will enter the region in question not merely from the arteries, but also from the neighbouring *capillaries* and *veins*; and while in a congested part a large quantity of blood flows with increased velocity through the vessels, at the seat of cupping a complete *stand-still*, a *stasis* is rapidly developed. The hyperæmia induced by cupping and local congestion have accordingly but a single point in common;

they both withdraw blood from the rest of the vascular system, and in this aspect the former has been already considered.*

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3. PASSIVE HYPERÆMIA.

Abnormal resistances to the capillary stream.—Gravity a resistance to the venous stream.—Hypostases.—Abnormal resistances to the circulation through the veins.—Consequences to the circulation in general.—Compensation of resistance.—Obstacles to compensation.

Description of the normal circulation as observed under the microscope.—Microscopic appearances in congestion, anæmia, engorgement.—Œdema of engorgement.—Explanation.—Diapedesis.—Signs of passive hyperæmia.—Consequences to the rest of the vascular system.—Consequences to the affected vessels.

Application to cardiac lesions.

Following the course of the blood-stream as it passes on from the arteries, the question : Can the resistance in the *capillaries* undergo changes capable of influencing the circulation ? first of all claims our attention. Now, please bear in mind that the lumen of the capillaries is normally liable to only slight variations. There are no muscular elements in the capillary wall, and though I willingly acknowledge the interesting observations on the contractility of the capillaries, as carried out first by Stricker and by Golubew,† and quite recently, in an especially comprehensive manner by Severini,‡ as well as by Roy and Brown,§ yet these authors have brought forward nothing to prove that occurrences of this nature exert any considerable influence on the capillary circulation. On the contrary, those who have made the living circulation the subject of prolonged microscopic observation are all agreed that the physiological resistances on the part of the capillaries appear to remain unaltered so long as the blood itself and the capillary walls continue normal. That changes in the constitution of the blood, on the one hand, and in the capillary walls, on the other, are capable of very considerably modifying the capillary-stream, you will learn in its appropriate place; but here we need only bear in mind those conditions that interpolate *abnormal* resistances in these minute channels, whether they arise within or from without these vessels. It is, in fact, nothing uncommon for true capillaries to be occluded by emboli of fine calibre, and isolated or entire groups of capillaries are no less commonly compressed by some agency or other acting from without. But having already thoroughly discussed the effects of an elevation of arterial resistance on the blood-stream, it would be superfluous to expound anew the analogous events in the capillaries. For, regarded from the point of view of hydraulics, a capillary network is indeed nothing more or less than a system of vascular tubes, anastomosing repeatedly with one another; capillaries not communicating directly and freely with other capillaries do not, as you know, exist anywhere, so that even the complete occlusion of one of them cannot be followed by any consequences except those attending the same occurrence in an artery having an anastomosis on the further side of the abnormal resistance; in other words, the branch capillary in which the plug is situated is shut off from the circulation, while the blood passes it by right and left, through the anastomosing channels, into the vein leading from the part. On the other hand, if it be, not a single capillary, but an entire area that is compressed, say by a tumour, we have again to deal with a condition precisely similar to that with which we became acquainted when considering rise of resistance in the whole of the ramifications of an artery; the affected part becomes *anæmic;* and as regards the locality occupied by the displaced blood, the laws formerly laid down are also applicable here.

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* On the subject of active hyperæmia consult Virchow's 'Handbuch,' p. 141. C. O. Weber in the 'Handbuch,' p. 29 ; Uhle und Wagner, p. 242.

† Stricker, 'Wien. akad. Sitzungsb.,' Bd. li, p. 16 ; lii, p. 379 ; Golubew, 'Arch. f. mik. Anatomie,' v, p. 44 ; Tarchanoff, 'Pflüg. A.,' ix, p. 407.

‡ L. Severini, 'Ricerche sulla innervazione dei vasi sanguigni,' Perugia, 1878.

§ Ch. S. Roy and J. Graham Brown, 'Journal of Physiol.,' ii, p. 323.

We may consequently turn without further discussion to the *veins*. In the venous system, as is well known, there is nothing that can be placed side by side with the resistance offered by arterial tonus. For though I do not absolutely deny the existence of a certain amount of venous tonus, there can be no question that it is incapable of opposing any perceptible hindrance to the efflux of venous blood; nor are we acquainted with any conditions, in particular with any nervous influences, by which the degree of this tonus may be raised or lowered. Even in the only venous area in which the effluent venous blood meets with resistances, and in which therefore it flows under a considerably higher tension than in any other portion of the vascular system, namely, in the *portal vein* and its ramifications in the liver, we know of no phenomena that might be referred with certainty to a tonus, or to an increase or remission of the same. Accordingly, as you see, a venous hyperæmia, fluxion, or congestion depending on a falling off in, or abatement of, venous resistance, is altogether out of the question. For even the local dilatations not at all uncommon in the venous system, the so-called *varices* or *varicosities*, present only an apparent diminution of resistance in the part concerned. It is of course unquestionable that dilatation of the venous channels favours the efflux of venous blood; but this gain will here be at once counterbalanced by the narrowing following immediately in front of the varix, and since the bed of the stream is enlarged without any alteration in the accelerating forces, there will simply take place, as in aneurysms, a considerable retardation of the blood-stream in the interior of the varicosity. But on the flow on either side of it, the presence of the varix can have positively no effect.

Purely quantitative rises in physiological resistance, such as play so important a part in connection with the arteries, cannot from the very nature of the case take place in the veins, and should occasionally a natural resistance to the venous circulation attain a pathological importance not usually falling to it, we have here to do, as you will immediately perceive, not with a rise of resistance but *with an enfeeblement of those factors which, in a normal condition, are calculated to overcome it*. I have now in mind *gravity*, which must undoubtedly oppose a certain amount of resistance to the flow in a contrary direction, *i. e.* to the upward venous stream, with the body in an erect position. You are acquainted with the means employed by the organism to overcome the resistance of gravity; they are, firstly, muscular movements in conjunction with the action of the venous valves, and, secondly, the aspiration of the thorax during inspiration. If it be true that even in a healthy individual whose calling involves long-continued standing, dilatations and varicosities are readily developed in the veins of the lower extremities, still more marked will be the effect of gravity in checking the flow when the muscular movements are feeble and the respirations shallow and infrequent. Yet the venous stream can still be tolerably well maintained provided the remaining factors concerned in the circulation fulfil their office regularly, *i. e.* as long as the tension of the arterial system is high and the heart acts vigorously, and in every respect normally. But as soon as the activity of the heart is impaired a danger arises from the influence of gravity, lest in those places where it opposes a natural impediment to the venous stream, its opposition may now no longer be overcome and the blood stagnate there. It is for this reason that patients whose lower extremities are paralysed, or who are condemned on account of fracture or the like to maintain a special position unvaryingly for a long time together, present a perfectly normal circulation throughout the entire body if they are in other respects strong, and especially if they are free from pyrexia; while, should they be attacked by a severe and protracted fever, serious circulatory disturbance only too readily makes its appearance. The same predisposition obtains in patients suffering from protracted pyrexial affections, in the course of which great muscular prostration takes place, as, for example, in the typhoid fevers. In the typhoid state, where the heart's action is so extremely enfeebled, where the muscular movements have practically ceased, where the thorax is but slightly distended by the frequent but very shallow inspirations, here, I say, gravity may become an impediment of such general importance that the venous stream fails, or almost fails, to overcome it. This applies, of course, only to the depending parts of the body—which these are, being determined by the attitude of the patient. In those who maintain the dorsal decubitus it will be the posterior portions of the lungs and the skin covering the scapulæ, sacrum, and calcanea; while in persons lying on the side it will be especially the region of the trochanters in which the so-called "*sinking hyperæmia*" or *hypostasis* occurs. It is obvious that the term "sinking hyperæmia" is a misnomer; for if the parts in question contain more blood than normal, this does not arise from the sinking of an especially large quantity into them, but is dependent on the fact *that the due amount is not conveyed out of them against the force of gravity.*

If we leave these complicated cases out of account, only one form of local disturbance arising from a change of resistance can, in accordance with what I formerly indicated, occur in the veins, namely, that *due to the interpolation of abnormal resistances.* True, this is an extraordinarily common occurrence. And the abnormal resistance may be situated either *external* to or *within* the affected vein. I shall mention only a few of the external variety; they are the pressure of articles of clothing or bandages, of tumours and exudations, of the pregnant uterus, or even of hard fæcal masses, of strangulation in hernia; then, too, cicatricial constrictions, under which head the process of hepatic cirrhosis is to be placed. Internal abnormal resistances are constituted by tumours starting either in the venous wall itself or in neighbouring parts, and growing into the interior of the vascular lumen, such as myomas, sarcomas, carcinomas. The highest degree of resistance is obviously that presented by the *occlusion* of a vein, such as is occasioned from without by severe pressure, most simply by a ligature, or from within by an obstructive thrombus or by a phlebolith completely filling the lumen.

The effect of this rise in resistance on the circulation in the veins may be characterised in a few words; *the blood must stagnate behind the resistance, i.e.* the tract lying to the rear of the obstacle is more strongly filled, and its tension is increased; at the same time *the flow is retarded by the resistance*, and consequently the velocity of the stream diminished. You see, these effects do not differ fundamentally from those ensuing on the interpolation of an abnormal resistance in an arterial channel. Nevertheless, a more accurate comparison of the details of the processes in each case at once reveals essential differences. You will remember that in considering the elevation of arterial resistance we laid special weight on the fact that the rise of pressure occurs in the united sectional area on the proximal side, and we found that a resistance in one of the femoral arteries causes an equal rise of pressure in the carotid and in the corresponding iliac. You will not expect a similar effect to follow an increase of resistance on the venous side. The elevation of pressure never extends farther back than the venous tributaries and capillaries of the area in which the narrowed vein originates, and is never communicated, I need hardly point out, to other more remote or neighbouring vascular territories. The value actually attained by the rise of pressure in the overloaded veins depends chiefly on the amount of resistance interpolated. On connecting the *vena femoralis* of a curarized dog by a ⊢ shaped cannula with the soda-manometer, and then, by means of a forceps with a catch, compressing the venous trunk a few centimetres in front of the cannula, between it and the heart, you at once observe a slow rise in the soda-column, as a rule not exceeding 80—100 mm.; the pressure remains constant for a time at this level, and then gradually sinks to the extent of perhaps 20—30 mm. That the rise of pressure attains no higher value is due simply to the presence in the leg of many other venous channels, through which the blood escapes into the cava, so that only a part of the united venous cross-section of the extremity has been occluded by the application of the forceps. Hence the venous tension attains much more considerable proportions if an india-rubber tube be placed around the entire limb in front of the cannula, but not including the femoral artery; the efflux of venous blood is thus completely blocked, and the venous pressure may now for a time almost equal the arterial in value, as was long ago determined by Poiseulle and Magendie.[*] All compensation is impossible here; if the retreat of the venous blood is altogether cut off, the tension in all the vessels of the leg must necessarily undergo a steady increase, and finally mount so high that it is only slightly less than that of the supplying arteries.

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[*] Magendie, 'Leçons sur les phénomènesphys. de la vie,' T. iii, p. 181.

Not so when other venous channels afford a free passage to the blood. I have just called attention to the fact that the pressure in the occluded *v. femoralis* begins after a time to fall from the elevation attained by it, and you yourselves without doubt have construed this as indicative of commencing compensation. This is, in truth, the case; but here, too, the further course of events in veins and arteries deviates widely enough in matters of detail, as the result of the different disposition of the arterial and venous systems. In the veins there are various arrangements that facilitate a compensation of the impediment. The slight physiological resistance of the venous system is favorable in this respect; the flexibility and thinness of the venous walls is also favorable, but the circumstance that the collateral channels are more amply developed in the venous system is above all a favorable factor; for example, one artery is very often accompanied by two veins. On the other hand, the inconsiderable tension in the veins is not, it is true, in itself promotive of compensation; still we have just now seen how capable this is of considerable increase, and how high a value it can reach as the result of an augmentation of resistance.

Thus a perfect compensation of increased venous resistance may very often be successfully effected. If, for example, an impediment be seated in one of the deep brachial veins, all the blood that cannot pass through the vessel will simply flow off through its fellow, since the rise of pressure on the distal side of the obstacle, although slight, is yet great enough so to distend the second brachial vein, which possesses practically no power of resistance, that the latter can accommodate and carry off the larger quantity of blood. No kind of detriment to, or derangement of, the circulation of the arm is to be anticipated under these circumstances. The valveless veins of the cavities of the body are especially adapted for compensation, and no event could be more indifferent to the circulation in the intestines than the occlusion of a branch of the *v. mesenterica*, or to the circulation in the genital organs than the obstruction of one or other of the pelvic veins. Yet in the estimation of these matters it will be prudent to calculate carefully the nature of the anatomical arrangements. Thus the venous valves, however desirable their presence and action where the circulation is normal, may occasionally render the compensation of a resistance absolutely impossible. The femoral vein is connected by a venous circle with the circumflex iliac vein, an arrangement apparently very favorable to compensation. And yet this circle is utterly worthless where an impediment is seated in the femoral, for, as Braune[*] has shown, the valves prevent any flow of a compensatory character. Add to this that the collateral channels, though on the whole very numerous, are far from *universally* present; thus the trunk of the portal vein is about the only vessel carrying away blood from the abdomen, and if this be narrowed, still more if it be occluded, there remain only some very diminutive, and in any case perfectly insufficient, vascular channels still accessible to the blood of the intestines, pancreas, &c. Braune has also shown that in man the *v. femoralis* is almost the only venous branch at Poupart's ligament which conveys the blood from the lower extremity into the abdominal cavity.[*] The like remark applies to the *v. renalis*, which also normally carries off so preponderating a quantity of blood from the kidney that its remaining vessels are quite thrown into the shade. This example is especially calculated to show where, despite all favorable conditions, the limits to the possibility of compensation are to be sought; a very small vein is not in a position to carry off instanter the blood from a large area, in the principal vein of which a considerable resistance is interpolated; and where there are actually several larger veins leading out of a part the complete obstruction of some of them will invariably tell as a resistance to the total efflux. There remains, as you see, a variety of cases in which an immediate compensation is not effected, in which, consequently, the abnormal resistance must exercise its influence on the circulation through the affected part. What is the condition of the circulation under these circumstances?

In order to arrive at a trustworthy decision on this question, it is expedient to subject a vascular area, in whose effe- [illegible] ins resistances are interpolated, to direct microscopic

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ne. 'Die Oberschenkelvene d. Menschen,' Leipsig, 1871.

examination. You have all of you already had an opportunity of observing under a low or a high power the finer details of the circulation through the web or the tongue of the frog, so that I may restrict myself to recalling very briefly to your memories the distinguishing and characteristic marks of the flow in the three kinds of vessels.* If you do not employ too high a power, it is almost everywhere possible to examine simultaneously arteries, veins, and capillaries in the same field of the microscope, and in any case it is advisable to seek out a spot in the tongue or *mb. natans* where you may directly compare the three sorts of vessels. The first thing which strikes everybody is of course the different *directions* of the stream, the direction in the arteries being the very opposite to that in the veins, and in the capillaries, as a rule, from the arteries to the veins; it is intelligible that on account of the reticular arrangement of the capillary vessels the direction of the stream through them will be by no means constant; indeed, it is nothing uncommon to find a complete cessation of movement for a longer or shorter period in a capillary channel, or even places where the direction of the flow is completely reversed for a short distance. Moreover, the eye is attracted by the difference in the *velocity* of the stream in the three kinds of vessels. The flow through the arteries is by far the most rapid, a character by which these vessels are usually first identified by the unpractised observer; next to this comes the venous stream, which, especially in the larger vessels, is very rapid, so that with a magnifying power of 150—180 one must be on the alert in order to catch the contour of a single blood-corpuscle. On the other hand, the stream is slower in the small veins, and in the capillaries the movement is, as a rule, so tardy that the individual corpuscles can be determined without any difficulty even when very high magnifying powers are employed. As a rule, I say, for in this point, too, the inconstancy of the capillary-stream is often enough apparent. If a group of capillaries be kept some time under observation the blood is occasionally seen to hurry suddenly through a number of these with increased rapidity; this continues for awhile, and then the stream becomes again slower and slower, till after an interval it reassumes the usual quiet *tempo* which has been maintained without interruption in the neighbouring capillaries. The cause of these variations is not far to seek; they certainly depend on alterations in the lumen of the afferent arteries, with respect to which I have already mentioned that alterations in their calibre are no less perceptible by the aid of the microscope than are changes in the larger arteries to the naked eye. A further difference in the stream in the arteries as compared with that in the other vessels consists, if I may say so, in its quality. The arterial stream is *pulsative*, and each systole may be recognised even in very small arteries by the rhythmical acceleration and retardation of the blood-stream; it is as though the column of blood received each time a powerful thrust impelling it forward anew. Such a rhythmical movement is unquestionably absent from the capillaries and veins in a normal condition; the stream is *continuous, homogeneous* in both. An especial interest attaches, further, to the condition of the *peripheral zone* in the three kinds of vessels. For in the arteries the core of red blood does not completely fill the lumen, and there always remains between it and the inner contour of the vessel wall an uncoloured layer of variable width, but measuring in general about 0·01 mm., in which a red corpuscle is never to be seen, a solitary leucocyte but extremely rarely, and where consequently nothing but *plasma* flows. In the veins there is also a similar peripheral plasmatic zone, but here we regularly find scattered colourless blood-corpuscles, which advance more slowly, indeed, much more slowly, than does the axial core of red corpuscles. In the capillaries, lastly, there is no special peripheral zone, for the lumen of these vessels allows at most of the passage of two blood-corpuscles abreast, and in the narrower channels admits only one. The corpuscles, red as well as white, are here everywhere in contact with the wall, and although it occasionally happens that they may be absent for a time from a capillary branch and only plasma flow in it, this appearance is quite inconstant, and as a rule quickly passes off, giving place under the eye of the observer to the ordinary stream of corpuscles. All other distinctions that may chance to be present fall into the shade in view of these striking differences in the flow through the three kinds of vessels; in particular the diversity in the *colour of the blood* is scarcely apparent, presumably on account of the thinness of the layers under observation.

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* Cf. Cohnheim, 'Virch. A.,' xl, p. 30.

If you desire to follow under the microscope the disturbances in the circulation hitherto discussed, nothing can be more simple. You need only roughly brush the tongue of a curarized frog, when the intense redness will not long leave you doubtful that a true arterial congestion has set in. A really magnificent spectacle now presents itself for microscopic observation. All the vessels, arteries, capillaries, and veins, are wide and strongly distended with blood; innumerable capillaries are perceptible at a glance where previously a few red-coloured threads were toilsomely sought for; and in all these vessels, small and large, the blood rushes on with the greatest rapidity, so rapidly, that even in the capillaries the eye in vain strives to catch the outline of a single corpuscle. Meanwhile the axial character of the stream in the arteries and veins is in no respect altered, or at most the peripheral plasmatic zone in the veins is also very poor in colourless corpuscles.

The microscopic demonstration of local anæmia may be most readily carried out on the same preparation. The application of pieces of ice need not even be resorted to in order to bring about contraction of the lingual arteries; it is sufficient simply to secure the tongue in position for a time, after having extended and stretched it a little, when whatever hyperæmia may at first have arisen, quickly gives way to complete anæmia. The arteries become narrow, the whole tongue pale. The eye has difficulty even in finding any except the larger vessels; but few capillaries appear to contain any blood; and where a considerable quantity of blood is still present, as in the arteries and veins, the flow is tardy, and even in the arteries the individual corpuscles can now generally be recognised. The rhythmical acceleration of the flow will naturally be conspicuous in proportion to the slowness of the stream. And as regards the arterial plasmatic layer, some colourless corpuscles occasionally arrive and remain in it for a time, while in the veins the number of leucocytes in the peripheral zone undergoes very considerable increase—facts which are easily explained by the tardiness of the blood-stream. The circulation continues in this state as long as the ischæmia lasts, without the occurrence of any other perceptible change in the vessels themselves or in their vicinity.*

In order next to prepare the frog's tongue for a microscopical study of the circulation in obstruction to the efflux of venous blood, it is only necessary to ligature both the large veins which, one on each side, convey the blood into the large venous trunk coursing along the floor of the buccal cavity; for some small veins situated between the principal lingual veins continuing pervious, these are sufficient to allow, though imperfectly, of the efflux of venous blood. Or you may bind a thread round the thigh of a frog, being careful to employ only moderate traction. Such pressure leaves the arterial circulation quite undisturbed, and by no means prevents the escape of venous blood, but simply impedes it. You may now observe the condition of the vessels in the swimming-web under whatever power you choose. What strikes you immediately after applying the ligature is the *decrease in the velocity* of the stream through the veins and capillaries. The blood cannot advance as formerly, and so *it stagnates*, as you can see quite plainly. This occurs first in the larger veins, then farther back in the venous tributaries, and very soon in the capillaries as far back as their union with the arteries. In the tongue, where the vessels are surrounded by very lax tissue, there takes place at the same time with the stagnation a gradual dilatation of the veins and capillaries; in the former vessels this may become really considerable. In the *memb. natans*, whose tissue is very dense and its meshes with difficulty distensible, the dilatation of the overloaded vessels is only trifling. But instead of this a new appearance is all the more rapidly developed here, namely, *the blocking of the vascular channels with blood-corpuscles*. The peripheral plasmatic zone of the veins disappears, for the red blood-corpuscles fill out the lumen till they come into contact with the internal contour of the vessel wall, and in the capillaries also there ensues a very dense accumulation of red corpuscles, owing to which the leucocytes present are completely concealed. The arteries alone have maintained their axial stream and their usual rhythmical flow. Thus the intense dark redness, which the organ presents to the naked eye, is found on microscopic examination to depend on a general distension of all the capillaries and veins with red corpuscles. These pass forwards in slow *tempo*, and where the hindrance to the escape of venous blood is considerable, at times with a clearly *rhythmical* movement, owing to the fact that the impediment can be more readily overcome during the systole than is possible during the pause. The dense accumulation of blood-corpuscles in the veins and capillaries can occur, of course, only at the expense of the *liquor sanguinis*. What becomes of the latter will soon be apparent. For you notice after a time that the tongue or swimming-web has become thicker, *tumefied*, which simply means that a certain amount of liquid has transuded into the tissues surrounding the vessels. True, a pretty long time, even several hours, must elapse before the infiltration of the tongue or swimming-web with transuded *liquor sanguinis* has reached such proportions as to impress the sight or touch as actual swelling. But please reflect in the first place how diminutive are the vessels with which we have to do in these localities, and above all consider that by no means the entire quantity of fluid transuding into the surrounding parts forthwith takes up its abode there. You are acquainted with the natural effluent channels for vascular transudations, I mean the *lymphatics*. There is, moreover, no difficulty in showing that the flow of lymph from a part is augmented when the escape of venous blood is impeded.* On introducing a cannula into one of the lymphatics on the outer side of the leg of a dog, an extremely small quantity of lymph flows off from the foot, scarcely a drop in several minutes, as long as the limb is at rest. On now ligaturing the principal veins conducting the blood out of the leg, or on surrounding the thigh just above the knee with a ligature, which must not be drawn too tightly, the lymph at once begins to drop from the cannula, so that you can now obtain in the same time as many (and indeed more) cubic centimetres of lymph as you formerly obtained drops. While the increase in the lymph-stream sets in immediately on applying the ligature, a tumefaction of the foot is only slowly and gradually developed during the space of several hours. Indeed it often happens in this experiment that the acceleration and increase of the lymph-stream makes its appearance, while the swelling of the paw does not take place, if namely the efflux of venous blood has been comparatively little interfered with. The inference is simple enough; a swelling, an infiltration of a part with transudation, an œdema from venous stagnation arises only when the lymphatics of the part are incapable of carrying off the whole of the transudation.

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* Cohnheim, 'Neue Untersuchungen über die Entzündung,' Berlin, 1873, p. 7.

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* Emminghaus, 'Arb. aus. d. Leipz. phys. Inst.,' 1874.

If we now seek to explain these events, which are so constantly associated with all hindrances to the return of venous blood, with *venous engorgement*, as it may be briefly termed, the key is to be found, it appears to me, in the behaviour of the arteries. We formerly saw that the effects of arterial congestion as well as of arterial anæmia extend on into the veins; how, in the former, the blood passes through the veins fed by the congested arteries under increased pressure and with augmented velocity; how, in the latter, the venous stream is feeble and slow in proportion to the amount of the impediment to the entrance of blood into the arteries. Now, how is it that a hindrance interpolated in the veins does not exert its influence back through the capillaries into the arteries, and here assert itself as arterial resistance, as a resistance with regard to the compensation of the effects of which we already know how the organism proceeds? The question is the more justifiable as something of the kind actually occurs in the lungs. You will recollect from our discussion of the cardiac lesions that stenosis of the left auriculo-ventricular orifice exerts an influence not merely on the pulmonary veins but as far back as the pulmonary arteries, so that the right heart dilates and hypertrophies owing to the resistance in the latter. And this ensues not only on hindrances to the entire venous efflux from the lungs, but in precisely the same way on abnormal resistances that have been interpolated in a part of the pulmonary venous channel. On introducing a manometer into the inferior principal branch of the a. pulm.

sin. in the dog, and then by means of a clamp occluding the veins of the superior lobe on the same side, or some of the veins of the right lung, you observe after a very short time a rise of pressure in the *a. pulmonalis* from 150 to 210 or even 220 mm. soda, while the tension falls at once to its original value on removing the clamp from the veins. You may repeat this several times on the same animal, and always with the same result, a most certain indication that this rise is dependent solely on purely mechanical relations.

You find nothing analogous to this in the systemic arteries. On connecting the *a. femoralis* of a curarized dog with the kymograph by means of a ⊢ tube you can satisfy yourselves that compression of, or the removal of pressure from, the *v. femoralis* has not the slightest influence on the tension; you may even include the whole extremity, the artery excepted, in an india-rubber tube, and yet the curve does not display the least alteration. When pulmonary and systemic arteries behave so differently in presence of the same interference, the cause must lie in physiological contrivances which are different in both. The tonus, as you are aware, fulfils the requirement, for it is practically absent from the pulmonary, and, on the contrary, plays a most important part in the systemic, arteries. The high pressure of the latter is due solely to the tonus, and it is this pressure that resists the venous stasis. Even where the venous efflux is completely blocked the tension of the veins does not, as we already mentioned, altogether attain the arterial level; still more will the venous pressure value fall short of the arterial if the venous flow is only impeded and not completely abolished. Hence the arterial supply continues, and the capillaries are placed in a dilemma, so to speak; on the one side the steady supply of arterial blood, on the other the resistance in the veins interfering with the due advance of the blood. The inevitable result is that *a portion of the liquor sanguinis seeks to escape laterally* through the walls of the thinnest vessels, *i. e.* from the capillaries and also probably from the smallest veins, *that consequently the transudation from these increases.*

Granted that, in accordance with this description, the increase of transudation is the result of the disproportion between the afflux of arterial and the efflux of venous blood, it directly follows *that the extent of the transudation is determined, not by the degree of venous resistance alone, but also by the amount of the arterial supply.* If the arteries conveying blood to a part are few and narrow you can understand that small and weak veins will be sufficient to secure an adequate escape of blood; and conversely, where the arterial stream is a very strong one, a moderate obstacle to the venous flow may cause marked stasis and transudation. On ligaturing in the rabbit the whole of the larger veins of both ears where they leave the root, and dividing the cervical sympathetic of one side, the ear whose sympathetic is uninjured will display no change whatever, while in the other a considerable doughy tumefaction is developed within a few hours. This œdema has in the abstract nothing to do with arterial congestion, and it was an odd misconception of Ranvier* that led him to urge so warmly the importance of the vaso-motors in this experiment. It is the hindrance to the escape of venous blood that is the sole determining factor in the œdema, and the congestion is influential only because it modifies so unfavorably the disproportion between afflux and efflux. But you will do well not to under-estimate the increase of the disproportion brought about by an arterial congestion. You formerly saw that the pressure in the *v. femoralis* rose, after occlusion of the central end, to 80—100 mm. soda. Let the steps of your experiment be precisely as before, and then divide the sciatic on the same side, and you will see the venous pressure mount to 280 mm. in a few minutes. To anyone who has witnessed this result it will not be astonishing that, after ligature of the *v. cava inferior* in the dog, only the hinder extremity whose sciatic is divided becomes œdematous, while its fellow betrays no trace of swelling. Yet the course of this experiment, by which Ranvier principally supports his view, is by no means constant, for it not uncommonly happens that œdema makes its appearance neither in the paralysed nor in the uninjured leg after ligature of the *v. cava inferior*, simply because the portion of venous blood passing from the hinder extremity by way of the *iliaca communis* into the *cava inf.* is not, in all [illegible] greatly preponderating quantity. The accessory venous channels of the extremities are, it is true, variable in number and size in different specimens, yet, even after occlusion of the *v. femoralis* and of the *v. ischiadica* as well, they are in any case sufficient to permit the easy efflux of all the blood forming the usual arterial supply of the limb. If one desire to really seriously impede the escape of venous blood from the extremity, these collateral channels must be included, and this is not accomplished by merely ligaturing some of the larger branches. You may, however, attain this object by introducing into one of the small cutaneous veins on the dorsum of the foot a paste of plaster of Paris so as to fill the larger veins, while an india-rubber tube tightly twisted round the extremity in the inguinal region cuts off for the time being all communication with the remaining systemic veins; as soon as the paste has set, *i. e.* after about ten to fifteen minutes, the tube is removed. Although the sciatic now thoroughly fulfils its function, a passive œdema takes place with absolute certainty; it is noticeable after a few hours in the neighbourhood of the *tendo Achillis*, and by the following day has spread to the entire extremity, so that this assumes a perfectly cylindrical form.* Moreover, this swelling, as I may remark in passing, is by no means permanent, but begins to decline as early as the third or fourth day, and the configuration of the limb operated upon is, after one or two weeks, in no way distinguishable from that of its fellow; nor need the experiment be attended by any other effects prejudicial to the animal.

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* Ranvier, 'Compt. rend.,' lxix, p. 25.

Accordingly, it is indubitable that the fluid of œdema is expressed from the capillaries and smallest veins as the result of a rise of pressure proceeding from the venous side, but it is *by no means pure plasma* that here filters through the capillary walls. In the transudation of stagnation the constituents of plasma are contained *in proportions and concentration entirely different to those of the plasma itself.* The saline contents and the so-called extractives accord tolerably completely in both; on the other hand, the transudation is invariably *poorer in albumen*, so that the dried residue is very considerably less than that left by plasma. But not merely less than that of the blood-plasma; it is always less even than the residue of normal lymph obtained from a part whose veins are pervious; while the latter usually contains between 4 and 5 per cent. of solid constituents, the lymph of stagnation falls to 3 or even 2 per cent.[*] It is to be noticed further that, as compared with normal lymph and still more with blood-plasma, this lymph possesses but a very slight tendency towards coagulation, and deposits only delicate flakelets of fibrin on lengthened standing. You will shortly learn that this feeble power of coagulation is immediately connected with the fact that the lymph itself is wont to be *strikingly poor in lymph-corpuscles*. *Red* corpuscles are also contained in the lymph produced in moderate engorgement, but usually only in small quantity, so that the transudation is represented by *a perfectly clear, thin, watery fluid*. Yet, when the impediment to the venous efflux is severer, it rapidly acquires a yellow tint, and a glance through the microscope teaches that this yellow colour depends *solely on the presence of great numbers of red blood-corpuscles*.

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* Sotnitschewsky, 'Virch. A.,' lxxii, p. 85.

The quantity of red corpuscles present in the lymph is greatest when the efflux of venous blood is *wholly prevented*, and microscopic observation of a part in which this condition has been experimentally produced will consequently be the best means of deciding how the red blood-corpuscles reach the transudation. The tongue or the swimming-membrane of the frog may again be most conveniently resorted to. To effect our purpose in the tongue, the organ, excepting the two lateral principal arteries, is to be bound round at its root; in the swimming-membrane it is generally sufficient to ligature the large femoral vein just before it enters the pelvis, or to apply the ligature surrounding the thigh somewhat more tightly.[†] All the phenomena previously observed in the slighter degrees of venous obstruction are also developed here, but much more rapidly and energetically. The retardation, the stasis of blood, and the plugging of all the veins and capillaries with blood-corpuscles, immediately become still more striking than before; the circulation through the entire vascular area regularly assumes

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[*] Emminghaus, 'Arb. aus d. Leipz. phys. Inst.,' 1874.

[†] Cohnheim, 'Virch. A.,' xli, p. 220.

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after a very short time a *rhythmical* character, and after no long period there arises a complete *va-et-vient*, because, owing to the vigorous resistance in the veins, the column of blood impelled forward at each cardiac systole recoils a space during the succeeding diastole. In the meantime the accumulation of blood-corpuscles in the capillaries becomes still denser and denser; already they are unable for want of room to maintain their usual position with their long axis in the direction of the stream, and are placed athwart it, the lumen of the capillary-tube being so stuffed with them that there is apparently no space for a single drop of plasma in their vicinity. And now the contours of the individual corpuscles begin to be lost, they seem gradually to become confluent, and, if we leave out of account the scattered colourless cells, the vessel is represented a few minutes later by *a homogeneous red cylinder*, in which no trace of motion is any longer observable.

In this state the vessels of the tongue or swimming-membrane remain for a time unchanged, as a network of homogeneous, dark-red cylinders. Suddenly you see *a red, roundish protuberance* appear on the external contour of a capillary; this increases gradually before your eyes, attains the size of quarter or half a red corpuscle, and then throws out lateral processes, likewise roundish, so that it comes to resemble a small mulberry. While the first protuberance thus goes on increasing from minute to minute, exactly similar ones rise up on other parts of the capillary network, and these soon become so numerous that after an hour has elapsed there is hardly a single capillary in the whole swimming-membrane whose contour is not beset with protuberances of this kind. Meanwhile the appearance of the interior of the capillaries is in no way altered; the external protuberances, however, grow to be large, roundish, knotted clumps, which now commence to fall asunder. For elliptical red bodies are gradually liberated from the compact and homogeneous mass; *these are nothing more or less than typical red blood-corpuscles.*

That simple *extrusion of the blood-corpuscles* through the vessel walls is actually the only operation concerned in this entire process is irrefutably proved by re-establishing the venous flow. Though the occlusion may have lasted several hours, when the ligature is removed from the tongue or femoral vein, the original conditions are after a short time restored. The disintegration of the cylinders commences in the veins and gradually passes back into the capillaries; one red corpuscle after another is set free from the apparently so cohesive homogeneous mass, and the lapse of a few minutes is sometimes sufficient for the re-establishment of the familiar spectacle of a brisk circulation in channels that till then appeared to be solid. Nothing now remains to indicate the previous coalescence of the corpuscles; indeed everything would be in the same state as before the application of the ligature, were it not that the protuberances and accumulations outside the capillaries witness sufficiently to the processes that have meanwhile taken place. For these clumps will naturally be unaffected by the restoration of the circulation; they are the masses of red blood-corpuscles that have been extruded from the vessels during the period in which the vein was obstructed, and only such corpuscles as were, if I may so speak, in the act of crossing the line at the moment the flow was re-established, are now in contact with the blood-stream. On observing the latter, one often sees how the free portion, smaller or larger as the case may be, remains perfectly at rest, while the portion within the capillary is incessantly driven against and lashed by the other corpuscles as they roll along; it thus acquires a rocking and oscillating movement, which mostly continues till at last the inner fragment is actually torn away from the outer.

Accordingly, I hope you will not have even a momentary doubt as to whether a laceration of the vessel wall has taken place here or not, but will at once be convinced *that the blood-corpuscles have actually passed through the undamaged wall.* It is a true *diapedesis* which we here for the second time meet with, and this time exclusively, or almost exclusively, of *red* blood-corpuscles. For should leucocytes form a constituent of the clumps, their proportion to the red blood-corpuscles is at any rate very trifling. The seat of the diapedesis is *the capillaries generally and the small veins,* while in the larger veins and *in the arteries no trace* whatever of such a process is to be observed.

Thus it is by diapedesis from capillaries and small veins that the red blood-corpuscles arrive in the transudation of a part, the venous efflux from which is extremely impeded. Yet to establish the facts of the process is very much easier than to explain it. Having become acquainted, through Recklinghausen and his scholars, with the so-called stomata of the endothelium, it will at once occur to our minds that a dilatation of the latter due to the increase of internal pressure might be regarded as the determining factor here. I myself formerly looked upon this interpretation as probable, and J. Arnold has, in a series of remarkable essays, lately come forward in support of a similar view.* Yet a really satisfactory explanation must take into account not merely the solid constituents of the transudation, but the substances in solution as well. It cannot be disputed, however, that orifices large enough to permit the passage of compact blood-corpuscles will much more readily allow the escape of *liquor sanguinis, plasma.* Now, the transudation of stagnation is, as we saw, by no means plasma, but is much richer in water and poorer in albumen ; and since, moreover, there is not the least reason to assume that the fluid is supplied by vessels other than those from which the corpuscles are set free, this stomata hypothesis fails, in my opinion, to explain the process. Rather, the circumstance that *the contents of the transudation in corpuscular elements may*, under certain conditions, *increase*, while *the substances in solution at the same time decrease*, clearly indicates that the living capillary wall is much more enigmatical in its nature than is a simple physical membrane.

But though the poverty of our knowledge, as I am ready to confess, at present renders the detailed explanation of the transudation of stagnation impossible, we still have abundant opportunities, by means of experiment and from our experience of disease, of satisfying ourselves of the truth of the foregoing description. On firmly applying a strong cord to the leg of a dog so as to include all the parts except the femoral artery, a perfectly red, watery, and very thin fluid, with hardly any tendency to coagulate, begins to drop from the cannula previously introduced into a lymphatic of the leg ; and if you ligature the ear of a rabbit at its root by tightly binding it round a cork, again excluding the principal artery, the resulting infiltration of the ear will be not merely œdematous, but at the same time hæmorrhagic; besides the red tint assumed by the tissues generally, you observe a multitude of small punctiform extravasations in the external and internal portions of the skin of organ. In precisely the same way, the kidney of a rabbit, whose *v. renalis* has been ligatured, swells in a few hours to twice or three times its natural volume, and is so permeated with hæmorrhages that it displays superficially and on section an almost black-red colour. Lastly, a lobe of the lung whose efferent veins are occluded, becomes within a few hours the seat of a really intense hæmorrhagic infiltration, occupying not only the alveolar septa but the alveoli themselves. That in man hæmorrhages as well as œdema are rapidly produced by completely obstructing the venous efflux has been shown by Auspitz,* who used phlebotomy bandages tightly applied to the forearm; and though *post mortem* we generally find the transudation of stagnation in the human subject clear or at most yellowish red, and very rarely bright red, this is undoubtedly due to the slow development of the processes producing engorgement, owing to which the possibility of the establishment of new effluents is assured,—a point to which I shall immediately return.

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* Arnold, 'Virch. A.,' lviii, pp. 203, 231 ; lxii, pp. 157, 487 ; Foà, 'Virch. A.,' lxv, p. 284.

Such then is the series of phenomena, which impediments to the venous efflux from a part of the body bring with them, unless compensated through the agency of other venous channels. Behind the obstacle, rise of pressure and retardation of the blood-stream make their appearance throughout the venous tributaries collectively, extending as far as the capillaries which discharge their blood into the constricted vein; as a result, stagnation and overfilling with blood, hyperæmia, set in. The arterial supply does not now cease, even when the occlusion is complete, but is at most diminished by the increase of resistance, and there is developed in consequence an increased transudation from the capillaries and smallest veins; this consists of a fluid poor in albumen and fibrin, which is more or less rich in red blood-corpuscles in proportion to the degree of venous resistance, and varies correspondingly in colour. Hence the picture presented by a part in a condition of *venous engorgement*, or as it is also called, of *passive* or *mechanical hyperæmia*. It is *redder* than normal, owing to increased fulness of the vessels, but the redness, as compared with that of fluxion, is more livid, bluish, or, to employ the *terminus technicus*, *cyanotic*. The darker hue is to be explained very naturally by the retardation of the capillary-stream, allowing as it does of a very perfect interchange of gases with the tissues. Moreover, it need hardly be mentioned that when the infiltration of the affected part, the œdema, is very pronounced, this will detract from the redness. For the second, and highly characteristic, sign of engorgement is *swelling*, which depends on the accumulation of the transudation in the meshes of the tissues of the affected part, and which has therefore a markedly *doughy* character in contradistinction to the pulsatile resistance of active congestion; pitting caused by the finger continues after the finger has been removed. The amount of swelling depends altogether, as we have seen, on the amount of the disproportion between afflux and efflux; thus in the so-called "sinking hyperæmia" there is practically no œdema on account of the feebleness of the arterial supply, while an extremity whose arteries are congested and whose veins are narrowed may assume really enormous dimensions. But how, or in what form the increased transudation shows itself, depends principally on the anatomical arrangement of the affected part. If it be one the meshes of whose tissues are distensible, a character most strongly marked in the subcutaneous cellular tissue as well as in the interstitial connective tissue in many places, the transudation collects in these meshes in so far as it is not carried away by the lymphatics; there arises what is called in general œdema, or, if confined to the subcutaneous cellular tissue, *anasarca*. On the other hand, if the affected vascular area borders on a free surface the transudation makes its appearance here and, according to circumstances, either flows in an outward direction or collects in a body cavity; in the latter case we speak of *free* or *cavity-hydrops*, or simply *hydrops*. This variety in the local disposition of the transuded fluid has of course no influence on its composition and properties. The third important symptom of venous engorgement, at least in peripheral parts of the body, is *reduction of temperature*. For the vessels of a hand, an ear, or of the dog's paw, the venous efflux from which is impeded, are so situated as to give off heat continuously outwards; but owing to the difficult and retarded flow in the capillaries the part is far from receiving its normal supply of warmth, and the cooling may thus amount to as much as several degrees.

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* Auspitz, 'Vierteljahrschr. f. Derm. u. Syph.,' 1874, Heft 1.

Our discussion up to this point has had reference solely to the condition of the circulation behind the abnormal resistance; but what, you will further ask, is the effect of a local hyperæmia on *the remainder of the vascular system?* The question may be readily answered. For in the portion of the vein beyond the impediment, between it and the heart, the *stream* must obviously *be retarded* and *the quantity of blood diminished*. The degree of this and the importance thus acquired by the condition depend on a variety of circumstances, on the size of the hyperæmic area, on the distance of the latter from the heart, and on whether other large veins inosculate a short distance beyond the obstacle with the vein whose stream is impeded by the abnormal resistance. In the veins lying immediately within reach of the suction-action of the thorax, it is practically immaterial, as regards the velocity of the blood-stream, whether a resistance is interpolated in their distribution or not, and when only a small area is involved it will scarcely be discoverable from the condition of the venous stream in advance of this that one source of its supply has been cut off. Not so, when the blood stagnates in very large veins and cannot escape from an extensive area. In the dog you may completely occlude the *v. cava superior* or the *cava inferior* below the liver, and yet no change of pressure is indicated by a manometer placed in the carotid; nevertheless on compressing the *cava inferior* between the liver and the heart you see an immediate and marked descent of the curve. In the rabbit the roominess of the abdominal vascular system is manifested still more strikingly. For a rabbit in which the portal vein is ligatured perishes within a few minutes, owing simply, as Ludwig long ago showed, to the rapid accumulation in the portal tributaries, and especially in the vessels of the intestines, of such a quantity of blood, that the remaining organs, in particular the brain, no longer receive the amount indispensable to life. But although nothing analogous occurs in this area in human pathology, inasmuch as the processes leading to occlusion of the portal vein are never of such acute character, the dangers of increased resistance in the large veins of other parts are but too well known to the physician. For it is unquestionable that the comparative emptiness of the systemic arteries in many cases where large pleuritic exudations exist is attributable to the action of the latter in bending and compressing the *v. cava inferior* at its point of entrance into the thorax.

You already see from these changes that the importance of venous engorgement varies extraordinarily in different cases. Yet when we have regard solely to the action of passive hyperæmia on the part of the body affected by it, it is a matter of great moment, as will be readily understood, whether the venous efflux is only impeded or completely at a standstill, and a great deal depends too on whether the stagnation is of long duration or only transitory. That a part whose venous efflux is permanently and completely barred must perish need hardly be stated expressly. For if the circulation in the capillaries be reduced to such an extent as we have seen it to be in the most extreme degrees of stagnation, if consequently the blood in these vessels has almost ceased to be renewed, metabolism must of necessity soon be at an end and the affected part perish. Yet such complete occlusion of the veins is met with in pathology only under very special circumstances, *e. g.* in incarceration of a loop of intestine in hernia or in obstruction of the *v. femoralis* at the level of Poupart's ligament. This latter example is especially calculated to show how manifold are the circumstances influencing the subsequent course of events. Not a few cases are on record in surgical literature in which perfectly healthy individuals have had the *v. femoralis* ligatured at Poupart's ligament on account of punctured or of gunshot wounds of the vessel; and almost without exception *gangrene of the* *remity* made its appearance during the days immediately wing the operation. Yet cases appearing to offer a most ing contradiction to these are no less frequently met with. Pieces of the vein have been excised during the extirpation of tumours of the inguinal region, and necrosis of the leg, that most unfortunate of terminations, is just as uncommon a sequela here as in the extremely frequent thrombosis of the femoral vein in this region. And yet the contradiction is only apparent. For only in the cases of the first category is the obstruction of the venous efflux really complete; *provided the distribution of the vessels be normal*, it is only here that occlusion of the femoral ensues. On the other hand, many of the thrombi are very far from completely occluding the lumen of the vein; and even when the thrombus is a locally obstructive one, it has not been formed suddenly, but requires for its development a long and often very considerable period. The same consideration applies to interference with the venous stream due to tumours of the inguinal region. While the lumen of the vessel was being gradually reduced, whether by the thrombus or by the growth of the tumour, new effluents from the affected area were slowly developing; small veins of the immediate neighbourhood conveying their blood in other directions were undergoing enlargement and taking up successively increasing quantities of the blood from the extremity, so that finally the complete closure of the principal vein formed no considerable impediment to the flow. It is in this manner that, under certain circumstances, even complete compensation can come about; but should this fail to be accomplished, the degree of venous stagnation will at any rate be so far diminished that the life of the part will be fully compatible with it. True, even moderate stagnation is accompanied by functional and nutritive derangements; these will, however, be discussed separately in connection with the different organs. On the vessels themselves the effect of engorgement which persists for a considerable time is permanent dilatation. The slight amount of tonus previously present in the veins has now completely disappeared, and such of the venous channels as have been long the seat of a passive hyperæmia remain dilated even after the removal of its cause. The walls of these dilated veins are not always thin; for distinct thickening of the intima, markedly sclerotic patches, may not infrequently be observed in veins whose walls have sustained for a long time lesions, a certain *pallor* of the skin, often associated with a *cyanotic* tint; we find, too, a cyanotic colouration of the internal organs generally, and above all, *watery effusions* wherever there is room for a transudation, *i. e.* anasarca as well as hydrops of the thorax, abdomen, and other cavities. Nor, lastly, is the *coolness* of the external parts absent in these heart-affections.

But these, so to speak, purely mechanical disturbances in all the organs are far from exhausting the prejudicial effects of uncompensated cardiac lesions on the mechanism of the circulation. For a moment's consideration at once shows that the quality and composition of the blood must ultimately suffer more or less as the result of the cardiac lesion. On simply reminding you that the flow of lymph from the *ductus thoracicus* into the subclavian will be essentially impeded by stasis in the venous system you will be able to judge how impossible it is for these cardiac lesions not to influence the constitution of the blood. Add to this, moreover, the pernicious effect of arterial anæmia and venous engorgement on the activity of the digestive apparatus and on the interchange of gases in the lungs; consider, further, that the function of the hæmapoietic organs, bone-marrow, spleen, &c., must undoubtedly deteriorate in consequence of the altered circulation through them, and you will certainly agree with me that the causes inducing morbid alterations in the composition of the blood in cardiac lesions are numerous enough. For the establishment and explanation of these alterations in detail our knowledge is, it is true, insufficient. But one point at least has already been placed beyond doubt —and I shall very shortly have to go into the matter more thoroughly—namely, that blood of normal quality is one of the desiderata most indispensable to the regular action of the heart and to the maintenance of the integrity of the vessel walls, a circumstance which in its effects renders heart disease one of the most painful affections to which the human organism is liable.*

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* On the subject of passive hyperæmia consult further 'Virchow's Handbuch,' p. 128; C. O. Weber, 'Handbuch,' p. 53; Uhle und Wagner, p. 255.

CHAPTER IV.

THROMBOSIS AND EMBOLISM.

Genesis of fibrin in the blood.—Maintenance of the blood in a liquid state dependent on the integrity of the endothelium.—Causes of alteration in the wall.—Standstill of the blood.

Primary and propagated, parietal, partially and completely obstructive thrombosis.

Embolism.—Its conditions and seat.—Recurring embolism.—Occurrence of thrombi and emboli in the different divisions of the vascular system.

Red and white thrombi.—Zahn's experiment.—Distinction between thrombi and post-mortem *coagula.*

Further history of thrombi.—Decolouration.—Organization.—Calcification.—Simple softening.—Yellow or puriform softening.—Micrococci.—Traumatic and spontaneous phlebitis.—Endocarditis ulcerosa.—Putrid softening.

Mechanical effect of venous thrombosis.—Mechanical effect of arterial obstruction.—Embolism of the a. mesenter. sup., *of the* a. iliaca, *and of the arteries of the leg.—Embolism of terminal arteries.—Obstruction of the portal vein and of the pulmonary arteries.—Hæmorrhage in arterial obstruction.—Mechanical effect of capillary emboli.—Fatty embolism.—Air embolism.*

Action of infective plugs.—Thrombo-phlebitis.—Venous fistula.—Metastatic foci.—Transportation of bacteria.

Thrombosis with the vessel wall intact.—Köhler's experiment.—Ferment intoxication.—Coagulation resulting from the contact of the blood with foreign bodies.

In the last few lectures we have discussed the condition of the circulation where the resistance on the part of the vessels is pathologically increased or decreased owing to abnormal alterations of their lumen. Now, the vessels are not merely the channels for the blood, but are still more intimately related to it by reciprocity of action. We know, in the first place, since Brücke's[*] celebrated experiments, that it is nothing but the continuous contact with the living vascular wall that keeps the blood fluid. As to the means whereby the vessel wall achieves this result, this is, it must be confessed, a question still open for discussion. True in the twenty years which have elapsed since Brücke's experiments, our knowledge of the chemistry of coagulation has become much more comprehensive and profound, thanks above all to the admirable researches of Alexander Schmidt.[†] We now know—and Hammarsten's[‡] most recent attack has not, so far as I can judge, shaken this view—we know, I say, *that fibrin arises from the union of two fibrin-factors, fibrinogen and paraglobulin, under the action of the fibrin-ferment;* and Alexander Schmidt has further shown that the fibrinogen is contained as such dissolved in the blood-plasma, and that, on the other hand, the whole of the fibrin-ferment and at least the greater part of the paraglobulin do not exist free in the *liquor sanguinis* but are derived from the *colourless blood-corpuscles*. Only by the disintegration of the latter, so Schmidt teaches, is the paraglobulin, and, still more important, the fibrin-ferment set free and their action on the fibrinogen made possible; so long, therefore, as the colourless corpuscles circulate uninjured in the blood, coagulation cannot be set up. According to this doctrine, which, as you will shortly hear, finds its strongest corroboration in pathology, the power of preventing coagulation possessed by the living vessel wall depends chiefly on its faculty of restraining the disintegration to which very many of the colourless blood-corpuscles rapidly succumb after the blood has escaped from the vessels. This does not of course imply that no colourless corpuscles perish during life, and that normally no free fibrin-ferment reaches in this way the circulating blood. On the contrary it has been actually demonstrated by Birk* in A. Schmidt's laboratory that free fibrin-ferment is at all times present in the circulating blood, though it is true in quantities constantly varying according to the intensity of the influences deleterious to the colourless corpuscles, whatever these may be. The fact that, in spite of this, coagulation does not ordinarily take place in the blood is explained by the power inherent in the living vessel wall of destroying or rendering non-effective small quantities of fibrin-ferment, a power which, as you will learn soon, reaches its limits only when *a large quantity* is introduced *at once* into the blood or is produced there. You will not, of course, be misled into supposing that the question—wherein this capacity of the vessel wall consists, has been solved by these highly important facts; rather the putting of the question has gained in precision.

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[*] Brücke, 'Virch. A.,' xii, pp. 81, 172.

[†] Alex. Schmidt, 'Arch. f. Anat. und Physiol.,' 1861, p. 545; 1862, pp. 428, 533; 'Pflüg. Arch.,' vi, p. 413; ix, p. 353; xi, pp. 291, 515; xiii, pp. 93, 146; 'Die Lehre von den fermentativen Gerinnungserscheinungen, &c.,' Dorpat, 1877.

[‡] O. Hammarsten, 'Nov. acta Reg. soc. scient. Upsal.,' ser. iii, vol. x, 1; 'Pflüg A.,' xiv, p. 211.

But however enigmatical this capacity of the vessel wall in its essential nature is, there can be no doubt that it is bound up with the *physiological integrity* of the wall. The wall is, however, a really complicated apparatus, and we may therefore profitably inquire, in which of its parts does the specific faculty reside? This has not, so far as I see, been up to the present strictly proved. Yet when we consider that the blood continues fluid in very small arteries and veins which possess neither adventitia nor media, that the same is true of the capillaries, which in their histological structure are exact equivalents of the endothelium of the larger vessels, the notion must involuntarily force itself upon us that it is the last, the *endothelium,* which prevents the coagulation of the blood. From this it follows directly that the blood will remain fluid in the vessels *as long as the endothelium is intact and performs its functions normally*; and it is for this reason that even in vessels whose media has undergone calcification or amyloid degeneration, or whose intima is in a condition of fatty degeneration or of sclerosis, no coagulation results, provided the diseased portions of the wall are covered by normal endothelium. I do not deny that it may appear at first sight strange to credit an apparently inactive, I might almost say lifeless, substance like this little membrane of completely flattened cells with a function so important; but this only shows again how cautious one must be in drawing conclusions based on impressions that have been derived from morphological characters alone. Moreover, whoever calls to mind Leber's* beautiful experiments, according to which the endothelium of Descemet's membrane alone prevents the passage of the *humor aqueus* through the cornea, will no longer feel that the importance ascribed to the endothelium on our assumption is exorbitant.

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* Birk, 'Das Fibrinferment im lebenden Organismus,' I—D, Dorpat, 1880.

But if this our view be correct; if, in order that the blood shall remain fluid, it must everywhere come into contact with an uninjured endothelium performing its functions normally, it logically follows from this that coagulation will take place whenever and wherever these conditions are not fulfilled. It is by no means uncommon in pathology for the blood to impinge upon parts of the vessel wall from which the endothelium is absent or where it is performing its function irregularly, or to come in contact with something else than the endothelium. Here belong all foreign bodies that have penetrated the heart or vessels, as needles, threads, echinococci, distomata; tumours that have broken through the vessel wall and so project into the lumen; and lastly that most frequently occurring and consequently most important condition, an already existing *blood-clot*. The circulating blood comes into contact with a clot of this kind wherever a thrombus has from some cause or other been previously formed. In the second place, however, it is essentially the contact with a blood-clot that brings about the spontaneous closure of all solutions of continuity of the vessel wall. From the aperture in the wall the blood is first of all effused into the surrounding tissues; here it necessarily coagulates, so that the blood circulating at the wound comes into contact with the external coagulum, and there arises at the place of contact a fresh coagulation which sooner or later occludes the opening. But the thrombosis following ligature, which one might be tempted to regard as the direct contrary of the so-called *traumatic* thrombosis, depends ultimately on the contiguity of the blood to something abnormal, since the intima is either ruptured by the ligature, and then crumples up, or its tissue and endothelial covering are bruised and mortify. This brings us immediately to other processes producing coagulation by killing the intima and endothelium, with subsequent shedding and removal of the latter; such are *necrosis* or gangrene of a vessel passing through a gangrenous region, the application of chemical substances which by their *corrosive* action kill the vessel wall; such are further *extremes of temperature*, heat and cold, and *drying* of vessels that may chance to be exposed to the air for some time. But a still more important part is played in pathology by the true *inflammatory* and *ulcerative processes in the walls of the vessels*; in consequence of them the endothelium, either alone or together with the intima, is separated and necrosed, as is seen in the arteries in *atheromatous ulcers*, in the veins in *phlebitis*, and in the heart in *endocarditis valvularis*, in the course of all of which coagulation of the blood is a complication attended by the severest consequences. Further, Ponfick* has lately shown that, in certain severe infective diseases, large numbers of the endothelial elements of the vessels undergo fatty degeneration and are shed, and it is possible therefore that such desquamated patches may, owing to imperfect regeneration of the endothelium, give rise to coagulation.

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* Leber, 'Arch. f. Ophthalm.,' xix, p. 87.

In addition to the foregoing factors there is yet another which, by reason of its extreme frequency, assumes a predominant importance for the entire question, namely, the effect of *retardation* or *standstill of the blood-stream* on the nutrition of the vessel walls. That retardation of the circulation plays a considerable part in coagulation was shown by Virchow, the creator of the doctrine of thrombosis and embolism, in his earliest pioneer investigations on thrombosis, and, following his lead, it for a long time passed as an axiom that the vessel wall prevents coagulation only when the contact of the blood with it is constantly renewed, or, in other words, only when the blood is in motion. A view of this kind was indeed rendered all the more possible, as it seemed to be supported not merely by pathologico-anatomical experience, but also by experiment. When in the dog or rabbit a large vessel is ligatured in two places somewhat removed the one from the other, the column of stagnant blood included by the ligatures is soon found to have coagulated. Yet anyone who repeats this simple experiment often, cannot fail to observe how dissimilar its course frequently is; the more perfectly the vessel is isolated from the surrounding tissues, and the more energetic the torsion with forceps and ligature, so much the more certainly and, in particular, rapidly does coagulation set in; while if the manipulation be as gentle and cautious as possible it may easily happen that coagulation will hardly have begun by the commencement of the following day. Moreover, Baumgarten* has lately pointed out that when the double ligature is applied under antiseptic precautions and the wound heals aseptically the included blood-column remains fluid after the lapse of weeks and months, and indeed, *may never coagulate*. These interesting facts, which Senftleben† was able fully to confirm in my institute at Breslau, unquestionably show that mere standstill of the blood is insufficient to bring about coagulation, and if the application of the double ligature without antiseptic precautions resulted regularly in the coagulation of the confined blood, clearly some additional agency must be engaged in producing by its co-operation this constant effect. This agency, as I have already pointed out, is the pernicious influence of stagnation on the nutrition of the vessel wall. When a vein or an artery is isolated from its surroundings and doubly ligatured, the circulation in its *vasa vasorum* must altogether cease, and the vessel wall after a time inevitably perish. It is this that is the immediate cause of the coagulation, which fails to set in after antiseptic treatment only because the death of the vessel wall is thereby deferred so long that new nutritive conditions have been established from without, in particular by the formation of new vessels.

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* Ponfick, 'Virch. A.,' lx, p. 153.

We shall henceforth, on the strength of these experimental results, refuse to recognise a pure thrombosis of stagnation in human pathology, though we shall adhere to the view that standstill of the blood is a cause, though an indirect one, of coagulation. On calling to mind the causes of retardation of the flow you will at once be able to judge under what circumstances a standstill of the circulation in the vessels can occur during life. It is far from necessary, especially in the veins, that the lumen should be completely obliterated before the blood can come to a standstill; stagnation and obstruction to the efflux alone suffice to bring about complete stasis, at least *in the pockets of the venous valves*. These have a tendency to flap together, owing to the internal pressure due to the resistance; the stream still continuing opposes this tendency, but is too feeble to force the valves back against the wall, so that the blood will very shortly stagnate in the valvular sinuses. The same thing will occur, it is obvious, in the transverse connecting veins of a stagnant area, even when these are valveless. And it will be especially liable to take place in the valveless veins when the capillary area from which they derive their blood is the seat of considerable resistance, as, for example, when the capillaries are compressed; that an increase in the venous tension will favour the stagnation is apparent. But in all these cases the standstill will be fatal to the nutrition of the vessel walls in proportion, on the one hand, to the extent of the affected venous area, and, on the other hand, to the defectiveness of the arterial circulation, for it is under these circumstances that the flow in the *vasa vasorum* will suffer most severely. This holds good above all of the extremely common general reduction of the velocity of the blood-stream as the result of the action of one of the factors hurtful to the heart's work, *e. g. feebleness* of the organ itself. Here it is the veins that are specially involved, and it is in this condition that the venous valves prove so effective in inducing standstill. Also there are parts of the cavities of the heart itself which are imperfectly emptied if the circulation is feeble, and to which consequently fresh blood fails to be supplied during every diastole. These are the *auricular appendices* and the *recesses between the trabeculæ carneæ* of the ventricles; since, however, the motive force developed by the right heart is in itself much slighter than that developed by the left, it is easy to understand that stagnation of the blood occurs more frequently on the right side. Now because in cases of this category the earliest clots were found with the greatest regularity in the above-mentioned situations precisely—the venous valves, the recesses of the ventricles, and the auricular appendices—and unaccompanied by any further observable morbid change in the affected localities, it was supposed that this so-called *marantic* thrombosis of Virchow afforded the best proof that the standstill of the blood alone suffices to bring about its coagulation within the vessels. Nevertheless the apparent integrity of these regions is delusive. On careful microscopic examination it is always possible to convince oneself *that the endothelium is absent* or more or less defective *at the seat of thrombosis.* Such defects are to be found in the venous sinuses as well as in the heart, and in the latter not merely corresponding to *myocarditic indurations* (which when specially extensive lay the foundation of *cardiac aneurysms*) but in the oft-mentioned recesses, the organ being in other respects normal, or at most fattily degenerated or dilated. To discover how these endothelial defects are conditioned in individual cases is difficult or impossible, yet their extensive distribution and special localisation appear to justify the view which sees in them an effect or a sign of defective nourishment of the cardiac or vessel wall. The loss of the endothelium may, it is true, be occasionally due to special more localised causes, *e. g.* in the heart to disease of isolated branches of the coronaries, or in a vessel to *compression* by a tumour or the like. The endothelial defects invariably present in *aneurysms* and *varices* in which thrombi have formed are also, if not a constituent phenomenon, at any rate a direct consequence of the vascular lesion on which the dilatation of the affected portion depends. From all which it follows, that in the marantic thrombosis as well as in the thromboses of compression and dilatation, in short in all varieties of thrombosis of stagnation, the defective action of the vascular endothelium is the intrinsic cause of the coagulation; thus in the cases adduced, coagulation of the blood occurring during life in the interior of the vessels may invariably be referred to the same factor. That retardation of the blood-stream and still more standstill of the circulation at the same time favours the occurrence of coagulation cannot of course be denied; yet this goes for nothing in the absence of such conditions as are actually in a position to produce coagulation; where no such are present, a thrombosis of stagnation cannot occur.

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* Baumgarten, 'Die sog. Organisation des Thrombus,' Leipsig, 1877.

† Senftleben, 'Virch. A.,' lxxvii, p. 421.

Where, however, one or, better, several of the factors just discussed are present, the blood passes from the fluid into the solid state, it coagulates, a *thrombosis* occurs. Following Virchow's example, this term is applied only to *coagulation taking place during life within the vessels*, while the products of *post-mortem* coagulation are called simply "*coagula*" or "clots." The thrombi may be advantageously distinguished as *primary* or *autochthonous*, originating at the spot where the causes producing coagulation act, and as *propagated*, depending on the deposition of fresh material on the original clot; the first variety is wont to be coextensive with the cause at work, *e. g.* the alteration in the wall, while the propagated thrombus has no such limits.

The thrombus, just as does a fibrinous coagulum in blood withdrawn from the vein, attaches itself to whatever solid substance lies nearest; this will as a rule be *the part of the vessel wall* where it originates, except when thrombosis around a foreign body is in question. Hence the thrombus may be designated *parietal* or *valvular* as the case may be, a terminology which of course is rational only so long as the thrombus does not fill out the lumen of a vessel, but simply adheres to the wall or valves, while a pervious channel still remains for the blood. But an autochthonous thrombus increases sooner or later owing to the power it possesses of exciting coagulation which has so often been dwelt on. The growth is effected by the deposition of one layer of clot after another, and thus the thrombus that was at first *partially obstructive* becomes after a time a *totally obstructive* one. But not merely is the lumen of the vessel completely filled out at the part in question, but the propagated thrombus increases in an axial direction also, and would finally bring about clotting of the entire mass of blood were it not that the power of preventing coagulation residing in the normal vessel wall sooner or later gains the upper hand. It will be readily understood that in the venous system, where everything is in itself more favorable to the coagulation of the blood, propagated thrombi usually extend much farther than in the arteries. Under favorable circumstances, *e. g.* in patients with lowered cardiac energy who have long been confined to bed, one often meets with thrombi continued from the ankles through the veins of the leg and thigh into the iliac veins and even the *v. cava inferior;* though it is true that in these cases the various valves may have afforded more starting-points than one for the thrombosis. On division or ligature of an artery the thrombus usually extends to the collateral channel immediately above it, but it may grow into the latter or may ascend in the ligatured vessel to a level far above this; the peripheral extremity lying in front of the ligature is as a rule empty and collapsed as far as the next lateral branch. On the other hand, when a vein is ligatured the propagated thrombosis is usually established in both directions, by preference, however, in the direction of the blood-stream, *i. e.* toward the heart. That the primary thrombi of the cardiac valves, ventricular recesses, and auricular appendices, can also undergo considerable enlargement by the deposit of new layers of clot, and may thus project as polypoid masses far into the cardiac cavities, need hardly be stated expressly.

Now, if you should come across a thrombus in any part of the vascular system and desire to account for its origin, the indication is evidently: always find out the cause of the *autochthonous* thrombus. If the relations just explained be borne in mind you will in very many cases readily succeed in establishing the seat of the primary thrombosis, whether it be a venous valve, a foreign body, or a tumour, a solution of continuity, or an ulcerated spot in the wall of the vessel in question. Yet there always remains a considerable number of cases where you meet with plugs, mostly short and of the obstructive variety, in places which seemingly do not present anything that might induce thrombosis, in perfectly smooth-walled arteries, for example, which are themselves branches belonging to a perfectly free and pervious vascular area and are surrounded by quite healthy tissue. How are these plugs to be explained? They have not really originated in the position they now occupy, nor are they in continuity with a primary thrombus seated elsewhere; *they are derived from some other portion of the vascular system from which they* *have been forcibly removed and transported by the blood-stream to the locality now occupied by them.* Such plugs are accordingly called *emboli*, as proposed by Virchow, and the entire process by which solid particles are transported by the circulating blood is named, *embolism*.

Virchow has shown, in a celebrated series of experiments, that the blood-stream can actually carry off with it solid bodies, even when these are large and comparatively heavy, such as bits of muscle, fibrinous coagula, india-rubber and even quicksilver, and has thus put it beyond doubt that thrombi, to say nothing of substances specifically lighter, such as fat-drops, colonies of bacteria, &c., are transportable. Bodies of this kind do not remain fixed in the heart during transport, though now and again they may be temporarily retained between the *chordæ tendineæ;* in fact not a single symptom marks the moment of their passage through the organ. Now, fragments of a thrombus may be crumbled off and hurried away by the blood-stream, either from the heart, whether they be seated on the valves, in the auricular appendices, or in the recesses or the apex of the ventricle; or from the arteries, whether the thrombi form part of the contents of an aneurysm or the coating of an atheromatous ulcer; or, lastly, and most frequently of all, from the venous system. In the heart and arteries the detachment of portions of the thrombi is most readily effected when the growth into the cardiac cavity or vascular lumen by secondary deposit has been considerable, while in the veins the determining factor is as a rule the relative positions of the propagated thrombus and the nearest pervious collateral. When the propagated thrombus grows from the occluded vessel into a large open vein, or when, on the other hand, the propagated thrombus in a large vein extends beyond the point of inosculation of a free lateral branch through which blood still circulates, the projecting point of the thrombus can, as might be anticipated, be torn away with the greatest ease, especially when its consistence and cohesion have been diminished as the result of softening—a matter we shall have to discuss presently. It is obvious that large as well as small fragments may be torn off, the largest from thrombi formed in aneurysms, the auricular appendices, or in very large veins. But the locality to which the detached thrombi are transported is determined by anatomical conditions alone. Coagula from the venous side of the vascular system, *i. e.* from the veins and the right heart, arrive in the *pulmonary arteries;* those from the arterial side, *i. e.* from the left heart, the systemic arteries, and the pulmonary veins are conveyed into the *aortic system;* while those from the portal tributaries reach the *branches of the portal vein* in the interior of the liver. Not only are these general fundamental rules of transport throughout the vascular system prescribed by anatomical structure, but the special paths within any given portion of the circulatory mechanism are also so prescribed. The cause determining the entrance of the embolus into one artery rather than another can, at least in the case of larger plugs, be as a rule satisfactorily determined, and is to be sought in the direction of the embolized vessel with respect to the principal trunk, *i. e.* in the angle at which it is given off, or in the relative calibre of the various lateral branches, or in some similar circumstance. Where the transport of the embolus appears to take place in opposition to anatomical laws, there are usually, as though to prove the rule, anomalies in the distribution of the vessels or in the heart. Thus I had quite lately an opportunity of observing a case of recent fatal embolism of one of the mid. cerebrals in a woman thirty-five years of age, where the valves of the heart, aorta ascendens, in short all the arteries from which an embolus might have been conveyed, were absolutely intact, while on the other hand an extensive thrombosis had occurred in the veins of the lower extremity. I had not, as you may suppose, at first the remotest idea of connecting the two conditions, till on more carefully inspecting the heart, I discovered a *foramen ovale* so large that I could easily pass three fingers through it. I could not any longer reject the possibility that here a thrombus carried off from the *v. femoralis* had on its way through the heart passed from the right into the left auricle and thence into the mid. cerebral.* But the more one sees how perfectly the anatomical conditions are maintained in the course of such events, the more difficult, it seems to me, will it be to make up one's mind to indorse the opinion of certain authors that in cases, it is true of rare occurrence, emboli may be transported against the blood-stream, as for example, out of the *vena cava superior* into the hepatic vein.* It is an old experience and capable of verification at any moment that particles, say, of cinnabar, granules of mercury, or even plugs of wax may be very readily driven by the positive pressure of an injection-syringe from the *v. jugularis* into the hepatic veins; but this proves nothing with respect to the ordinary circulation, and I should, for my part, regard such an occurrence as very improbable, so long at least as the blood-stream through the portal vein is unimpeded.

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* Litten ('Virch. A.,' lxxx, p. 381) describes a similar case, in which the *foramen ovale* being patent, a thrombosis of the right auricle was believed to have formed the starting-point for repeated embolism throughout the systemic vessels.

Naturally the emboli are arrested during transport in larger or smaller vessels according to their size; the largest of all in the principal branches of the pulmonary arteries, for example, or, on the other side, in an *a. renalis* or *iliaca communis,* or even in the *aorta descendens* at its point of bifurcation. On the contrary, the smallest plugs not only penetrate into the capillaries, but may pass through a capillary area, where these vessels are comparatively wide, and afterwards be arrested in capillaries of narrower calibre; thus after injecting finely divided chromate of lead or cinnabar into the *v. jugularis* it is not at all unusual to come across particles in the loops of the renal glomeruli or in the capillaries of the brain. That direct communication of an artery with a vein, where it happens to occur, would favour such skipping of a capillary system by emboli is at once apparent. Lastly, emboli whose diameter is less than that of the finest capillaries can of course pass everywhere unhindered, and when they nevertheless, perhaps after long wandering, remain fixed anywhere, this is due to circumstances other than their size, *e. g.* to the roughness of their surface or their accidental adhesiveness or the like.

On the other hand, the larger emboli will mostly be arrested, as is natural, in those situations where the vascular lumen undergoes narrowing, especially therefore at the place of origin of large lateral branches or at the point of bifurcation of arteries. Thus nothing is more common than for emboli to be found "*riding*," as it is called, or seated upon the bridge formed by the bifurcation of a large artery, and so to obstruct both its branches at their commencement. For when you consider that the emboli are wedged into the part in question by the power of the blood-stream and are arrested here only because they are too large to pass through the succeeding tract, you will find it natural that they should in the large majority of cases belong to the *completely obstructive variety;* their capacity to cause obstruction is especially favoured by their softness, which allows of their being perfectly adapted to the mould formed by the lumen of the vessel. Yet it occasionally happens in isolated cases that an embolus remains fixed athwart the stream behind the point of bifurcation without completely occluding the lumen. In such cases the blood-stream will at first continue to flow by it, but as a rule only for a short time, since the embolus itself induces fresh thrombosis so that the partially obstructive plug now comes to be a completely obstructive one. Before it has gone so far, however, small pieces may be torn off from the embolus and then carried further by the stream, thus leading to a kind of *recurrent* embolism.

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* Heller, 'D. Archiv f. klin. Med.,' vii, p. 127; Wagner, 'Allg. Path.,' p. 281.

A second variety of recurrent embolism is that in which at first smaller and afterwards larger emboli are transported into the same vascular area, when the former are arrested in the most remote, the latter in the larger proximal branches. This is by no means a rare event, and the probability of its occurrence is supported by what often happens in experiment, where several plugs, though introduced at pretty long intervals in succession into the jugular, travel into the same branch of the pulmonary artery. After all that has been said it need hardly be mentioned specially that an embolus which is completely obstructive from the first may be enclosed by fresh thrombi, the deposit taking place very commonly on the central side but also on the peripheral.

Let us see if we cannot deduce from the foregoing certain rules as to the occurrence *intra vitam* of coagulation in the different parts of the circulatory apparatus. We may expect to find 1, in the *heart* only *thrombi*; these will occur above all on inflamed valves and *chordæ tendineæ*, also in partial cardiac aneurysms, further, in the recesses between the *columnæ carneæ* (so-called *globular vegetations*), while in the auricular appendices and in the apex of a ventricle when dilated very large polypoid thrombi may be met with. 2, In the *veins* we find *thrombi*, parietal and valvular, partially and completely obstructive, primary and propagated; only in the branches of the portal vein within the liver can emboli as well as thrombi occur, the former by transportation from the portal tributaries, the latter, *e. g.* round distomata or in the immediate neigbourhood of hepatic abscesses. 3, In the *arteries* both *thrombi and emboli* occur; thrombi in aneurysms, after ligature and injuries, after destruction of the endothelium by ulcers or the like; emboli in the pulmonary arteries, conveyed from the right heart and the systemic veins, in the systemic arteries from the pulmonary veins, the left heart, and the aorta or its larger branches. It is often difficult to determine the nature of a plug met with in an artery. The size is not alone a differential mark; for, as you know, large as well as small pieces may be torn off from a thrombus and transported elsewhere, and you know too how much the true primary thrombi may vary in their dimensions. There are, however, some other characters on which reliance may be placed. You should first examine whether any local cause of coagulation be present at the seat of the plug, *e. g.* considerable narrowing, an aneurysm, an injury to the arterial wall, or an ulcer. The presence of one of these factors makes thrombosis extremely probable, although the possibility that an embolus had been arrested at this particular spot must, of course, be admitted. If, on the other hand, the plug be situated at the point of bifurcation of an artery or origin of a lateral branch, if it *rides*, as I formerly explained, you may unhesitatingly pronounce it an embolus. Another fact of great importance is that a thrombus, in accordance with the history of its origin, as will soon be explained at length, always *adheres* to the wall, at any rate where it is autochthonous, and as a rule too farther on where it is propagated. The embolus, on the contrary, sits loosely in the lumen or at least is unconnected with the vessel wall so that it very readily falls out on cutting open the vessel in which it is contained. This it is true holds good, as I may add at once, only of a still *recent* embolus. If a considerable time has elapsed since its entrance adhesion to the vessel wall has usually meanwhile been established, and it is now often quite impossible, even by a most careful examination of the preparation, to decide whether thrombosis or embolism has taken place. Here you may occasionally be able to obtain a clue from the clinical history as well as from the consideration of the other conditions present, which in any case are deserving of careful attention. For obviously you cannot with perfect certainty determine that embolism, say of a systemic artery, has occurred, unless you are at the same time successful in making out its source. Should all other resources prove of no avail you may be assisted by pathologico-anatomical experience, which teaches that both emboli and thrombi are found in the brain, in the coronary vessels of the heart, and in the arteries of the extremities, while, on the other hand, in the arteries of the lungs, intestines, kidneys, and spleen, thrombi are comparatively rarely met with. 4, In the *capillaries and the smallest arteries and veins*, the so-called capillary arteries and veins, one may expect to meet very small emboli, but thrombosis is also possible here. The latter is, however, a peculiar case. The contents of the capillary vessels will remain fluid, it is evident, only as long as the endothelium lives and fulfils its function; but since the wall of these vessels is built up of endothelium alone, death of the endothelium is equivalent to necrosis of the entire vessel. In short if we leave injuries out of account, capillary thrombosis or, as it is also called, *capillary stasis*, occurs *only in mortification of the capillary vessels*, a process which, as you will hear later, invariably involves at the same time the death of the tissues supplied by the capillaries in question. *Propagated thrombosis never takes place in the capillaries* apparently because their lumen is too minute to allow of the withdrawal of any part of the liquid threads from the influence exerted by the wall in checking coagulation. For the rest, the characters distinguishing between embolism and thrombosis of capillaries are very obvious; a capillary embolism can never be anything but minute, while a thrombosis will properly be coextensive with an entire capillary area of smaller or larger size.

Now, what is the appearance of a thrombus, and what becomes of it? A thrombus is nothing but coagulated blood, and must therefore have at first the same appearance. Yet two modes of origin should be kept distinct from the very commencement *according as the thrombus has been formed while the blood was at rest or in circulation.* Blood drawn from a vein and allowed to remain perfectly undisturbed in a cylindrical vessel assumes during coagulation a form quite different from that acquired by it on being vigorously whipped with a rod of whale-bone; and so it is also within the vessels. In the former case you see a blackish red coagulum whose volume is at first exactly the same as that of the blood from which it is formed, and which later also, when the loss of serum by expression has more or less diminished its size, preserves its dark red colour because it encloses the whole of the red blood-corpuscles. It is otherwise with whipped blood; the more vigorously you whip and set it in motion with the rod of whale-bone, the more certain are you to secure the deposit on the rod of viscid fibrinous masses, which are at first red but gradually become paler till in the end they may be scarcely yellow; these last contain only a few red blood-corpuscles from which they may indeed be altogether freed. In complete accordance with these results, you find in a vein which has been doubly ligatured, a *red*, voluminous thrombus; on the contrary, a thrombus occurring on an ulcerated portion of the aortic wall is colourless, or as it is called, *white*. Zahn* has taught us, in a very interesting series of experiments, how the formation of the latter, the white thrombus, may be followed directly under the microscope. If you injure one of the larger arteries or veins in the extended tongue or mesentery of a curarized frog, *e. g.* by laying a small crystal of common salt close to some part of the vessel, you at once observe that the portion of the inner surface of the wall corresponding to the crystal becomes covered over with colourless blood-corpuscles, whose number constantly increases as the salt melts; soon there are three or four layers of densely packed colourless corpuscles adhering to the interior of the wall, and the clump continues to grow by the accession of fresh white corpuscles from the blood as it flows by. The whole of this portion of the lumen is now occupied by a mass of densely packed leucocytes amongst which hardly a single red corpuscle can be recognised; and the blood-column is completely interrupted by the white motionless plug, which is distinguishable even by the naked eye as a white gap. But the course of events is not always so typical. At another time, especially if the salt has lain upon instead of near the vessel, you see the deposit of colourless corpuscles progressing not merely from one but from all points of the circumference towards the interior of the vessel, and nothing is more common than for some red corpuscles to be hemmed in and held fast by the leucocytes. Nor do by any means all the plugs become so large as to fill up the entire lumen; many of them are mere colourless prominences, protruding into the blood-column and narrowing the passage there. On steadily observing such a plug, consisting exclusively, or of a majority, of white corpuscles, you may sometimes see the entire mass caught by the blood-stream, next begin to waver, and then suddenly swim away; whereupon, if it has been seated in an artery it is arrested sooner or later according as it has continued entire or been broken up, or if in a vein it disappears from observation. At the seat of the plug, however, there is formed as a rule a fresh, perfectly similar, but mostly smaller mass, provided at least that the action of the salt has not been too intense. Yet this is not always the fate of the white or mixed coagula; some of them succeed in maintaining their position in opposition to the power of the blood-stream, when it is usual for them to increase longitudinally in a centrifugal as well as in a centripetal direction by repeated accessions of white corpuscles. There is now no difficulty in tracing their further destiny. The clump of cells, at first slightly lustrous, soon becomes finely granular and contracts a little, while at the same time the contours of the individual elements become less distinct. This appearance becomes more marked during the next few hours till after at farthest twenty-four hours the cell-boundaries are for the most part lost, so that we have now before us a faint, dull grey, feebly refracting, finely granular mass, in which it is as a rule impossible to render the nuclei visible by means of acetic acid or of colouring matters having an affinity for the nuclei; in saying which we of course leave out of account a variable number of colourless cells that are still preserved and clearly recognisable in the midst of the finely granular mass. Exactly the same appearance is observed, as is well known, in fibrin obtained from the blood by whipping; it presents a granular feebly refracting mass in which some white corpuscles and a certain number of red are included. True the red blood-corpuscles are usually more numerously represented in the fibrinous masses obtained by whipping than in the plugs produced artificially in a vein or artery; but this is to be attributed to the fact that the movement occasioned in the glass by means of the rod of whale-bone, cannot be compared in point of uniformity with that communicated to the blood in the vessels of the living organism by the circulation. It was precisely this experimental production of thrombosis I had chiefly in mind, when I held out to you the prospect that the most recent views of Schmidt on the nature of coagulation would be corroborated by pathology. For the part played by the colourless corpuscles in coagulation cannot, in my opinion, be more significantly demonstrated than by these experiments, in which the eye of the observer is enabled to follow the transformation from the liquid into the solid condition *pari passu* with the disappearance of numbers of colourless blood-corpuscles.

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* Zahn, 'Virch. A.,' lxii, p. 81.

You need only call to mind the history of the origin of thrombi, and you will be able at once to infer when and under what conditions a *white* and when a *red* thrombus will be met with. The third variety, the *mixed* thrombus, is not at bottom dissimilar to the white, differing only in the presence of a certain number of included red corpuscles. Whenever the circulation is maintained during the formation of the thrombus, there arises the white or at most the mixed variety. It follows from this that all thrombi deposited in large vessels in consequence of alterations in their walls must be *white;* and the same holds good of all coagula upon foreign bodies, inflamed valves, as well as of all propagated thrombi. But the domain of the white thrombus is still more extensive. For the thrombosis by which the closure of a wound of a vessel is brought about must of necessity be colourless, since here if anywhere coagulation takes place with the blood in circulation. And lastly, it is quite conceivable that in cases where only a portion of the blood flowing through a vascular cross section has come to a standstill, as happens in marantic thrombosis of the venous valves and of the recesses between the *columnæ carneæ* of the heart, the coagulum may also be white or at least mixed. At any rate experience constantly teaches that it is so; the globular vegetations are always uncoloured, and the venous valvular thrombi are also far from being red. You see that *an extremely large majority of all the thrombi found in the body are white or mixed*, and there remain but a few cases in which the conditions necessary to the formation of a red coagulum are presented.

Thus most of the thrombi coming under observation have a *white* or else a *grey* or *greyish-red* appearance, a character that often cannot be clearly made out until loose *post-mortem* clots have been removed; for the latter have a decided tendency to become deposited on the thrombi. Between these and thrombi you will never have the least difficulty in distinguishing. A *post-mortem* clot is nowhere adherent to the vessel wall, but if care be taken may be drawn out of the aorta, cava, &c., in the form of a very long branched cord. On the contrary, every thrombus is, as already stated, *adherent* at least at its place of origin, and as a rule beyond this. A fresh embolus, it is true, is not, as you are aware, adherent; but a *post-mortem* clot certainly cannot be confounded with it, inasmuch as the embolus usually takes the form of a comparatively short fragment terminating centrally and peripherally in a blunt rounded-off extremity. A *post-mortem* clot is moist, shining, tolerably elastic, possesses a perfectly smooth superficies, and is often in parts markedly "buffy;" a thrombus on the contrary is from the first decidedly drier and more compact, and, provided it has attained a moderate size, is always *stratified*. This last property, which is due to the deposition of successive layers during formation, is therefore one of the most characteristic of all. A *post-mortem* clot is never stratified, while in a thrombus this feature is so well marked, *e. g.* in large thrombi such as form in aneurysms, that a section through its thickness gives the impression of a mass consisting of a system of fibrinous lamellæ. To the stratification it is also to be attributed that a thrombus from which a piece has been torn off terminates in a *stair-like* extremity; for otherwise the end of the plug, especially that directed towards the heart, is, as a rule, conical. Among the microscopic characters of a thrombus the most striking is its richness in more or less well-preserved colourless blood-corpuscles, a peculiarity pointed out long ago by Virchow, and one which has been fully explained by the history of its development. There is no such wealth of white corpuscles in the red thrombus; rather red and colourless corpuscles have here the same numerical relation as exists in blood drawn from a vein. Nevertheless, you will hardly ever run the risk of confounding a red thrombus with a blood-clot, if you only bear in mind the conditions under which alone the formation of red thrombi can take place.

Every thrombus is wont, after remaining for a time in the condition described, to pass through certain metamorphoses without our always being able to specify the circumstances on which their occurrence depends. One of the commonest is the *decolouration* of the red constituents of the plug. This takes place slowly and gradually, the red corpuscles shrinking in part and in part disintegrating, while a portion of their colouring matter is diffused into the vicinity and resorbed, and the remainder (as will be more minutely discussed in another place) transformed into *hæmatoidin* or *pigment*. It is the occurrence of such pigments in many older thrombi that affords the most certain proof of the actual presence at a previous date of red corpuscles and accordingly of a decolouration having taken place. Yet this process is at present far from playing the part in the theory of thrombosis which was ascribed to it at a time when the detailed history of the formation of thrombi was as yet imperfectly known. When we nowadays meet with a yellowish-white or whitish-grey thrombus we need not have recourse to decolouration in order to understand the absence of colour, however necessary this appeared while red was held to be the original colour of every fresh thrombus. At present therefore this process comes into consideration only in the very uncommon red thrombi and in addition in the red portions of the mixed variety; whereby, it is true, the latter may come to resemble a white coagulum so closely that a decision as to the original nature of the thrombus is sometimes only possible, if at all, by a microscopic demonstration of residues of pigment and hæmatoidin.

But with respect to the importance and effects of a thrombus it makes no difference whether it be decolourised or not, nor has this any influence on its subsequent fate. Its destiny is utterly different according as the thrombus becomes *organised* or *undergoes softening*. By organisation the thrombus is, so to speak, metamorphosed into *solid vascular connective tissue*. This interesting occurrence has for many years attracted the attention of surgeons and pathologists and has been interpreted very variously in harmony with the general scientific views prevailing at the time.* At present we may venture to regard it as certain that the thrombus itself is in no way engaged in the tissue-formation. Its cell-elements, the remaining leucocytes and whatever red blood-corpuscles may be present, perish; while the granular fibrinous material composing the great bulk of the plug contracts and, if not completely resorbed, is finally greatly reduced in volume. Nor is it, so far as I know, any longer a matter of dispute that a chief part in the production of the connective tissue taking the place of the thrombus is to be ascribed to the newly-formed blood-vessels, which, whether originating from the *vasa vasorum* of the affected vein or artery or from the vessels of the adventitia and surrounding connective tissue, grow into the interior of the thrombus. It appears that the advance of new vessels takes place most vigorously and abundantly at those places in the vessel wall where the intima has been severed, for example, by a ligature, or has been otherwise lost. In this way the thrombus becomes *vascularised*, an event, as you will learn later, which is always the first and most indispensable step in every pathological formation of connective tissue. The question: How does this new connective tissue with its cellular elements arise? still forms the subject of an animated discussion. After all previous authors had sought to answer it by examining the more or less fully-formed tissue, Senftleben attempted to arrive at a definite conclusion by varying the conditions experimentally. He took pieces of large veins or arteries ligatured at both ends, from rabbits which had been dead several days and introduced them into the abdominal cavities of living rabbits, after having previously disinfected them by prolonged exposure to the vapour of carbolic acid, and in some cases after having in addition placed them for a time in water at 50° C.; *the lumen of these dead vessels also became filled with a vascular connective tissue consisting of the most typical spindle-cells.* This experiment, which, oddly enough, Baumgarten* was unable to confirm, but which nevertheless, as I can assure you, almost never fails if the necessary precautions be observed, proves at any rate that organisation of the thrombus may be effected *without the active participation of any portion of the vessel wall, and solely by the intervention of wandering cells that penetrate from without.* But now consider further the perfect accordance between the microscopic pictures presented by the dead and the ordinary object—an accordance so perfect that it is quite possible to confound the one with the other; and you will hardly hesitate, I think, to agree with Senftleben in his conclusion that the formation of connective tissue in the thrombus takes place in exactly the same fashion *intra vitam*, and is not due to proliferation of the endothelium of the vessel, to which Baumgarten, Raab and others are inclined to ascribe the result. The time elapsing before organisation is complete is extremely variable; in the most favorable cases vascularisation is very advanced as early as the sixth or seventh day, and in a few weeks the portion of the lumen formerly occupied by the thrombus is filled with a delicate, slightly gelatinous, vascular connective tissue; while at other times organisation has hardly gone beyond its earliest beginnings even after the lapse of months.

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* B. Reinhardt's 'Path.-anatom. Untersuchungen, herausg. von Leubuscher,' Berlin, 1852, p. 42; O. Weber, 'Handb. d. Chirurgie,' i, 1, § 139, 1865; Waldeyer, 'Virch. A.,' xl, p. 391; Bubnoff, ibid., xliv, p. 462; Thiersch, 'Pitha-Billr. Handb.,' i, 2, p. 531; Tschausoff, 'A. f. klin. Chirurg.,' ii, p. 184; Kocher, ibid., p. 660; Durante, '. Wien. med. Jahrb.,' 1871, p. 321, 1872, p. 143; Cornil et Ranvier, 'Manuel d'histolog. patholog.,' Paris, 1873, p. 550; Czerny, 'Virch. A.,' lxii, p. 464; Riedel, 'D. Zeitschr. f. Chirurg,' vi, p. 459; Auerbach, 'Ueber die Obliteration der Arterien nach Ligatur,' I.-D. Bonn, 1877; Baumgarten, l. c.; Raab, 'Arch. f. klin. Chir.,' xxiii, p. 156 (contains numerous references to the literature of the subject); Foà, 'Arch. p. le science méd.,' iii, No. 4; Nadiejda Schulz, 'Ueber die Vernarbung von Arterien nach Unterbindungen und Verwundungen,' I.-D. Bern, 1877; Pfitzer, 'Virch. A.,' lxxvii, p. 397; Senftleben, l. c.

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* Baumgarten, 'Virch. A.,' lxxviii, p. 497.

But we have good reason to regard such organisation as a favorable termination of thrombosis, for one thing, because the other dangers, especially those accompanying the possible softening of the coagulum, are thereby set aside; and, in the second place, because organisation is the first step toward the partial re-establishment of the circulation through the affected vessel. In this direction the vascularisation of the thrombus has already a certain value; for although, as you know, the *vasa vasorum* do not receive their blood from the vessels in whose walls they course—a rule holding good not merely of the veins but equally true of the arteries—yet there is very commonly established between the newly-formed vessels of the thrombus and the still open lumen of the artery or vein a direct connection, sufficient to allow of a certain degree of communication between the proximal and peripheral portions of the vessel. Of far greater importance, however, is the fact that the product of organisation, the newly-formed connective tissue, begins after a time to contract, this being as you will afterwards learn, a perfectly constant characteristic of all recently developed connective tissue. Should this contraction take place simultaneously from the centre towards the periphery in the whole circumference of the vessel there must arise *a new lumen*, a kind of central canal in the midst of the organised thrombus. But more often the contraction ensues without any such regular correspondence to all the radii of the vascular tube. It is easy to conceive that the thrombus may adhere more firmly to some portions of the periphery than to others, and when under such circumstances the tissue commences to contract it will be most forcibly withdrawn from precisely those places where its attachment is lax. Thus there originate narrow, laterally-placed channels, several of them sometimes in the same thrombus; these do not, however, all pass continuously from one of its extremities to the other; some of them are interrupted here and there. The organised thrombus has now acquired a certain resemblance to a sponge, and the implicated portion of the vessel to a venous sinus, inasmuch as its interior is also spanned by bands of connective tissue in the form of incomplete bridges and septa. For this termination of organisation the term "*sinus-like degeneration*" was selected by Rokitansky. It is more commonly met with in veins than in arteries, and its really typical seat is the confluence of the two *v. iliacæ* to form the *v. cava inferior*, in which situation a perfectly sieve-like lamina sometimes remains as the solitary residue of an obstructive thrombosis. The blood can again pass through the apertures in this lamina, *i. e.* through the channels above described, though the stream will not, of course, be so free as before the formation of the thrombus. A certain amount of restoration is, however, invariably secured thereby, and when the contraction of the organised tissue becomes somewhat considerable, restoration may even be so perfect that the whole disturbance is reduced to a trifling stenosis of the vascular lumen.

In this respect a second termination to which thrombosis is liable, namely, *calcification*, admits of no comparison with the foregoing. We shall have to defer the account of its origin till later; it is sufficient here to establish the fact that lime-salts are occasionally deposited in a thrombus, as a rule after it has undergone considerable contraction through loss of water and siccation. This process of calcification, to which amongst other things the *phleboliths* owe their origin, is, it is true, far from resulting in a restoration of the original conditions; nevertheless it may be classed with the favorable metamorphoses of thrombi, if for no other reason, because it for ever prevents the occurrence of softening.

For the *softening* of a thrombus is the termination which has always been most dreaded by physicians and surgeons, and with reason. In itself there is nothing strange that a plug, if it do not organise, should after a time lose its consistence, and the transformation of the innermost layers of a thrombus, these being furthest removed from the vessel wall, into a thin, pulpy, oily fluid is in truth a most common event.

If the thrombus in question be red, a red fluid is found, to be distinguished from normal blood by its browner hue, and especially by the fact that well-preserved biconcave red blood-corpuscles can no longer be observed in it on microscopic examination. If, on the other hand, the softened thrombus belong, as it usually does, to the white or to the mixed variety, the fluid derived from it will have a yellowish white to reddish yellow colouration, and reminds one of pus, all the more so as not only its creamy or viscid slimy consistence, but also the presence in it of smaller or larger numbers of round-cells, as shown by microscopic examination, lends it an unmistakable likeness to this fluid. The softening and liquefaction in the interior of a plug is in many cases more readily recognised by the sensation of fluctuation communicated to the examining finger than by the most accurate inspection, for very often the outermost layers can in no respect be distinguished from a solid and firm thrombus-mass, and only after an incision has been made is the fluid discovered. Such a condition may be observed with extreme frequency in venous thrombi of all kinds; further, central softening is but rarely absent from the globular vegetations of the heart, which, indeed, for this reason formerly received the name of *purulent cysts*; it is also very common in thrombi of the auricular appendices, as well as in the larger thrombotic deposits on the cardiac valves; and lastly, it is met with often enough in the parietal thrombi of the aorta and other large arteries. In a decided majority of these cases nothing noteworthy or unusual is displayed either by the surface of the thrombus or by the locality in which it is situated, be this a vein, an artery, or the wall of the heart; and we are therefore justified in concluding that the character of the entire process is not essentially modified by the central softening. Accordingly it would appear quite appropriate to term the softening in these cases *simple*, and we should have no reason whatever for regarding this simple softening as an undesirable alteration, were it not that the separation of smaller or larger fragments is thereby facilitated, and thus the chances of embolism enhanced.

But the constitution of the softened thrombus is not always so innocent. In certain cases the wall of the vessel in which it is sit[illegible]d to be in a condition of *most severe puru-*

lent inflammation, while, wherever particles of the thin pultaceous mass are conveyed, there ensues the most violent inflammation, terminating in suppuration or even in necrosis. Yet the most careful inspection of the liquefied material reveals no distinction whatever between it and the product of simple softening; it is the same yellow to reddish yellow, tenacious, slimy or creamy liquid, which indeed bears such a striking likeness to true pus that we really cannot be surprised at its having for a long time passed as such. True we now know, since Virchow cleared up the anatomical history of the process, that this liquid is not pus, and cannot therefore be, as Cruveilhier supposed, the product of the inflamed vessel wall; we know definitely that it is by no means pus, but merely pus-like, *puriform, not purulent*, for the simple reason that it is nothing else than *the product of the softening and liquefaction of a thrombus*. Yet you will have all the more reason to ask, Whence then arises this striking difference? To what is it to be attributed that the liquefied material of a thrombus proves as a rule so perfectly innocuous, and in some cases so exceedingly pernicious? The behaviour of this material, resembling as it does that of an albuminoid substance undergoing rapid decomposition, does not allow of our attributing the liquefaction of the thrombus to the absence of vascularisation, although this may perhaps suffice for the explanation of simple softening. Some other agency must evidently be at work here, some agency whereby the softening acquires its specific, we need not hesitate to say, *infective* character. Microscopic examination acquaints us with this other agency inasmuch as it shows that *lowly organisms, schizomycetes*, are present in these cases.

The name *Bacteria* or *Schizomycetes*[*] is applied to a group of organisms, which, though some of the smallest beings of which we have any knowledge, possess by reason of their immensely wide distribution an importance in the entire economy of nature that cannot be too highly estimated. For many of the commonest and most important *fermentative processes* depend on them, as we have learned chiefly from the unsurpassed researches of Pasteur; and no less dependent on them are all the processes of *decay* and *putrefaction* taking place in the organic world. The bacteria effect these results by abstracting during vegetation certain elements from the substratum in which they have settled so as to bring about the decomposition of the latter. Thus they are in the fullest sense *exciters* of fermentation and putrefaction, which however favorable may be the other conditions, never set in in the absence of these organisms. Moreover, notwithstanding their extraordinary minuteness, the schizomycetes are capable of producing important effects even in a comparatively short time, owing to the really incredible capacity for multiplication inherent in them. This reproductive capacity is so characteristic of them, that it may be looked upon as the best and surest criterion of their vitality; and if you suspect the presence of living bacteria anywhere you need only introduce a minimal quantity of the suspected material into a suitable nutritive fluid and allow it to remain exposed to a moderate temperature in order, from the appearance or non-appearance of turbidity, to arrive at a definite opinion as to the lawfulness of your suspicion. For, provided the nutritive material is suitable, the only conditions necessary to the action and multiplication of the bacteria are a certain mean temperature and a certain degree of moisture; with too high or too low a temperature, or in a perfectly dry state, they do not thrive and multiply, although their capacity for development is not always forfeited in consequence. This being the position of affairs, it is clear not merely that there would be no obstacle in the way of the invasion of the living animal body by bacteria and of their subsequent development therein, but that

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[*] Cf. Pasteur, 'Annal. d. chim. et phys.,' 1860, p. 1; Compt. rend., lvi, p. 1189, &c.; F. Cohn, 'Beiträge z. Biologie der Pflanzen,' Bd. i, Hft. 2, p. 127; v. Recklinghausen, 'Verh. d. Würzb. phys.-med. Ges.,' 10 Juni, 1871; E. Klebs, 'Beiträge zur path. Anat. d. Schusswunden,' Leipsig, 1872; Heiberg, 'Virch. A.,' lvi, p. 407; Eberth, ibid., lvii, p. 228; Köster, ibid., lxxii, p. 257; Billroth, 'Untersuchungen über Coccobacteria septica,' Berlin, 1874; C. Hueter, in 'Pitha-Billr. Hdb.,' i, Abth. ii, pp. 1—127, 'D. Zeitschr. f. Chir.,' i, p. 91; C. Weigert, 'Ueber pockenähnliche Gebilde in parenchymatösen Organen und deren Beziehung zu Bacteriencolonien,' Breslau, 1875, 'Berliner klin. Wochenschr.,' 1877, Nos. 18, 19; R. Koch, 'Unter-

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suchungen über die Aetiologie der Wundinfectionskrankheiten,' Leipsig, 1878; Naegeli, 'Die niederen Pilze in ihren Beziehungen zu den Infectionskrankheiten und der Gesundheitspflege,' München, 1877; Perls, 'Lehrb. d. allg. Path.,' ii. p. 112.

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the most favorable conditions would be presented by it, did not *the competition of the vital metabolism* there await them. This is the really decisive point; the possibility of the settlement and multiplication of whatever bacteria may be in question depends on their ability to withstand or overcome the competition of the animal metabolism. Now the fact, established experimentally, above all by Nägeli, that where several species of bacteria are together present in a nutritive fluid it is usual for only one of them to develop vigorously, leaves no doubt that the vital energy of the various schizomycetes is very unequal, and it is simply in consequence of this that by no means all species of bacteria are met with in the living body, though many, it is true, are found there. The true bacteria of putrefaction do *not* belong to the number of those possessed of this developmental capacity, and although innumerable multitudes of them are at all times present in the digestive tract, they are never found in the tissues or vessels of the organism while the body is in a physiological condition. The case is altered when individual parts have lost their vitality and undergone necrosis; it is then, as you will hear later, something very common indeed for bacteria of putrefaction to colonise them and there to undergo the most active development. Since, however, a thrombus is material arising from the death of colourless blood-corpuscles, so that its vital metabolism is certainly extinct, there is nothing *a priori* against its occupation by bacteria of putrefaction, which as the result of their subsequent development would exert their specific chemical effects. Nevertheless, the bacteria found in a thrombus undergoing *yellow* or *puriform softening* but very exceptionally belong to the species designated after Ehrenberg *Bacterium termo*, which we have good reason to regard as the true exciter of putrefaction. Those met with here belong rather to the group at present usually called *spherobacterium*, or still better *micrococcus*. These are spherical granules whose size may vary within certain limits, but is always very minute. Their finer relations may be most conveniently studied in any putrefying meat-broth, where they are invariably present, though, as you will observe, they are not themselves the exciters of putrefaction. On examining a drop of such liquid, you will find innumerable *single* micrococci, then very many arranged in pairs or forming short *chains*, and, lastly, closely-packed *masses* held together by a kind of gelatinous material. These masses, to which F. Cohn gave the name *zooglœa*, are always the most striking objects in the microscopic picture, owing not so much to their bulk as to the extremely characteristic *shagreen-like* quality lent them by the precise uniformity in size and regularity in relative position of the individual granules. But these masses of micrococci or, as they are also called, *colonies*, have a peculiar importance in pathology *in that by their aid an absolutely certain diagnosis becomes practicable.* During the last decade, which has been so extraordinarily fruitful for the study of bacteria, microscopical technique has, it is true, been enriched by numerous expedients calculated to give precision to our methods of recognising them; thus Weigert* has shown that the micrococci of the colonies are strikingly and vividly stained by most of those colouring matters that stain the cell-nuclei; and R. Koch† has recently taught that single bacteria occurring in a liquid can also be coloured if the liquid have been previously allowed to evaporate from the slide. But despite this undeniable progress and the greatly increased facility given to such investigations by the most recent improvements in our microscopes, and especially by Abbé's illuminating apparatus, I still hold the attempt to determine with perfect certainty the presence or absence of *isolated* micrococci in a given locality for an extremely nice undertaking. I, at least, should not like to trust myself to pronounce a definite opinion as to which amongst the innumerable fine and coarse granules occupying the field of the microscope when a drop of puriform pulp from a thrombus is placed under it are albuminoid products of the disintegration of the thrombus, and which are micrococci. We shall therefore confine our attention to the colonies, which can be positively diagnosed. These you will seek in vain in thrombi, wherever seated, that have undergone *simple* softening; they are absent from the marantic thrombus or the thrombus of compression of the veins, as well as from the parietal thrombus of the aorta, from the globular vegetations of the recesses of the heart, as well as from the ordinary thrombi of the auricular appendices. On the contrary, every drop of pulp from the puriform thrombus of our second, infective category is wont to contain a more or less large number of unmistakable colonies. These are, furthermore, invariably found in that form of *endocarditis* called, with reference to its course, *endocarditis ulcerosa* or *maligna;* and, indeed, the masses are here as a rule much larger than in the puriform venous thrombi; they even infiltrate the proper substance of the valve, sometimes to such an extent that the swelling and increased volume of the latter must in great part be attributed to them. Lastly, a search for these colonies in the *emboli* torn away and carried off from a thrombus that has undergone yellow softening or from an ulcerated valve will hardly be undertaken in vain.

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* Weigert, "Ueber pockenähnliche Gebilde, &c.," 'Virch. A.,' lxxxiv, p. 275.

† R. Koch, in Cohn's 'Beiträge z. Biol. der Pflanzen,' Bd. ii, Hft. 3, p. 402.

To prove that the micrococci actually confer on the thrombi that malignant and infective character to which the purulent inflammation in the vicinity affords ample testimony, something more is needed than the mere demonstration of the presence of colonies. Does it appear in itself at all inconceivable that the bacteria may have colonised the altered and disintegrated coagula and purulent foci only because they there found a soil peculiarly suited to their growth and development? Yet a number of facts of undeniably great importance make against such an hypothesis. Thus it is not uncommon, especially in the case of persons who have died in consequence of ulcerative endocarditis, for an opportunity to be afforded of observing in different portions of the body emboli composed of colonies of micrococci surrounded by tissue which is still perfectly uninjured and intact, while no embolic abscesses occur in which colonies are wanting; a fact permitting, it seems to me, of but one interpretation—that the invasion of micrococci always precedes the inflammation. Still more important are the observations which have been accumulating for a considerable period with regard to the *almost epidemic occurrence of suppurative phlebitis* and pyæmia in hospitals, and the apparent transmissibility of these processes; how strongly these observations favour the notion that lower organisms are engaged cannot of course be adequately appreciated by you till the nature of the virus of the infective diseases has been thoroughly discussed. Lastly, the view maintained by us is greatly strengthened by the circumstance that puriform softening of thrombi with consecutive phlebitis and its sequelæ, which at one time constituted the severest scourge of every surgical ward, has since the introduction of the *Listerian treatment of wounds* undergone the most astonishing decrease. For even if the importance of many of the details of Lister's method be still an open question, one fact at least is firmly established—namely that one of its undoubted effects consists in the creation, by means of dressings charged with material destructive to bacteria, of conditions highly unfavorable to the settlement and especially to the further development of the schizomycetes.

Should you agree with me in considering these reasons sufficient, and accept the presence of the micrococci as the determining element on which the striking difference between the softened thrombi of each category depends, you will regard the question: *Whence, and by what path, have the bacteria reached the thrombus?* to be one involving issues of the utmost fundamental importance. This question is readily answered when the affected vessel is in direct contact with an open wound or ulcerated surface exposed to the atmosphere. For should the surface of a wound not be protected by suitable means, the ubiquitous bacteria which establish themselves everywhere make no exception here; indeed they find in its secretions and still more in the pus a soil extremely favorable to their subsequent development. Yet, however easy it is to understand that micrococci may arrive in a thrombus in a stump after amputation, in a puerperal uterus, or in the vicinity of carious patches of bone or of diphtheritic ulcers of the intestine, the circumstances on which the infection depends are very far from being always so apparent. So it is in the first place in cases of *spontaneous phlebitis*, as it is called in contrast to the *traumatic* form. As a rule the affected individual has also some kind of wound, ulcer, or abscess. He dies with all the signs of evident pyæmia, and no supposition seems more plausible than that a thrombus seated in the veins bordering on the wound or ulcer has undergone softening and puriform disintegration.

Yet you explore all the veins of the region without coming across anything of a suspicious character; the lumen is everywhere pervious and the vessels themselves quite unaltered; this cannot have been the starting-point of that fatal disease to which the remaining post-mortem appearances so unmistakably point. Continue your search, however, and you suddenly come upon the typical puriform softening in the venous plexus of the pelvis or in the muscular veins of an extremity in other respects perfectly intact. If even in these cases there is apparently no continuous path between the softened thrombus and the point of entrance of the micrococci, wherever this may have been, still less can there be any question of such continuity in *endocarditis ulcerosa.* Nevertheless you must from the start dismiss all thoughts that the bacteria could have arrived in the thrombus or even the body in any other manner than *by penetration from without.* I am well aware that authors of good repute—to say nothing of some utterly unscientific persons—defend the opinion that micrococci and similar structures may arise from the disintegration of animal cells; yet micrococci have never so far been observed in a locality where all chance of their entrance from without was excluded.[*] We shall therefore unconditionally maintain the view that micrococci are true and unmistakable living organisms; and the only question is whether their presence in the thrombus is to be referred to an express invasion from without or to an accidental accumulation or collection of microbes which are constantly present as isolated individuals in the juices and tissues of the physiological organism. The latter alternative is evidently bound up with the possibility of establishing the presence of living bacteria with a developmental capacity in the interior of the healthy body, a process of proof which for reasons readily understood cannot be carried out by microscopic examination, but only by having recourse to experiment. But the only experiment which can here be decisive, the examination namely of any portions of the body which, being absolutely protected against the access of schizomycetes from without, have been placed

[*] This also applies to the experiments of Weissgerber and Perls, 'Arch. f. experiment. Path.,' vi, p. 113, who found numbers of emboli composed of micrococci in the renal vessels of the rabbit after compression of the v. renalis.

under conditions favorable to the development of bacteria —this experiment, I say, is beset with very considerable difficulties; and you will, therefore, not be surprised to hear that many tried experimenters have been thwarted in their attempts to overcome them. At present it may be looked upon as proved *that the juices and tissues of the animal organism when in a healthy condition contain no examples of bacteria capable of development and multiplication.* This holds good not merely of the bacteria of putrefaction whose presence in the living body was long ago disproved by the telling experiments of Traube and Gscheidlen,* but of the bacteria in general, as was demonstrated chiefly by Meissner† in some excellent experiments. From this, however, it inevitably follows that only by express invasion could the micrococci have reached the thrombus. Nor in the great majority of cases is the gate by which they have succeeded in effecting an entrance into the body far to seek. For it is not only in spontaneous phlebitis that, as already mentioned, we have to do mostly with individuals who have somewhere or other a wound, a purulent focus, or the like; one of these same conditions is as a rule present in patients affected with *endocarditis ulcerosa;* and how large a contingent is furnished to this disease by *puerperæ* has long been known. In fact there remains only a very small number of cases of this kind in which, despite a most painstaking examination of the entire body, we fail in finding a pathological gate of entrance; and only here are we compelled to resort to the hypothesis that the micrococci have penetrated from physiological tracts, mainly perhaps from the respiratory.

We shall now give a brief *résumé* of the points recently discussed. Perhaps the most frequent of all changes undergone by thrombi which do not organise is softening and liquefaction. Though this process is generally innocent and harmless, in a number of cases the liquefied thrombus pulp is proved by the condition of the surrounding tissue, above all by that of the vessel wall, to be one of the most infective substances with which human pathology has to deal. This poisonous character is due to the presence of micrococci which usually gain entrance from a part in direct contact with the vessel containing the thrombus. Sometimes, however, they are conveyed from a remote purulent, ulcerated, or wounded spot; while in rare cases the physiological respiratory or digestive tracts are perhaps their places of entrance. After a short journey through the blood- or lymph-vascular channels, they arrive in the thrombus and rapidly undergo further development in this favorable soil. It is possible, indeed probable, that the disintegration of the thrombus is due to the action of these schizomycetes; it is, at any rate, certain that the capacity of the disintegrated material to excite inflammation depends on them alone. These are the cases for which Virchow introduced the term "yellow" or "puriform softening" in contradistinction to the simple form; and though we are at present perfectly well aware that a yellow and thoroughly pus-like liquid also results from simple softening of a white or mixed thrombus, and the name has therefore lost the meaning which Virchow intended it to convey, we shall nevertheless do well to retain this simple expression now that it has become naturalised. Your attention has been repeatedly called to the complete dissimilarity existing between the schizomycetes causing puriform softening and the bacteria of putrefaction. But as though to put this to the test, and so to convince any of you who may be unable to get rid of the idea of their identity, there is a genuine undoubtedly *putrefactive softening* which occurs in thrombi seated in veins that are in contact with intensely putrefied surfaces; thus it is in the uterine veins in putrid endometritis, in the veins of the leg in gangrene of a stump after amputation, and in the pulmonary veins in *gangræna pulmonum*. In these happily rare cases the thrombus is transformed into a discoloured, ichorous, completely putrid pap, giving off the *odoriferous products* inseparable from every true putrefaction. Such odoriferous products, however, are entirely absent from a thrombus undergoing ordinary yellow softening, and the diseased foci arising under the influence of puriform plugs in the vessels are also free from evil smell. Thus an *a fortiori* proof is afforded that yellow softening is altogether different from putrefaction, and is rather a *specific bacterial effect* or, better expressed, *an effect of specific bacteria*—of bacteria which, it is true, are often found associated with the bacteria of putrefaction. At least it would be easier on the latter assumption to understand how it is that yellow puriform softening should also take place in thrombi seated in veins bordering on a focus of putrid decomposition, just as often if not oftener than does the putrefactive softening.

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* Traube und Gscheidlen, 'Berl. klin. Wochenschr.,' 1874, No. 37.

† Cf. Rosenbach's report, 'D. Zeitschrift für Chirurg.,' xiii, p. 344, the only authentic account of these highly interesting experiments which has appeared up to the present. Burdon Sanderson, 'Quart. Journ. of Microscop. Science,' Oct., 1871, has arrived at the same conclusion.

For the rest it is obvious, without further explanation, that both yellow and putrid softening favour the separation of particles from the thrombus, and thereby the occurrence of embolism. On meeting with a puriform embolus in an artery, you may even venture, as a rule, to conclude unhesitatingly that it is derived from a softened thrombus, although there is nothing in principle against yellow softening of a simple compact embolus under certain circumstances, just as the embolus may under other circumstances organise.

Having followed till now the various destinies of a thrombus we are confronted with a further task, namely, the discussion of the import of thrombosis and embolism to the organism. We naturally first turn our attention to the purely *mechanical effects* on the blood-stream, the more so as we have already dealt so thoroughly with the local disturbances of the circulation that this aspect of the question may be dismissed after comparatively brief consideration. At this advanced stage of our discussion I need hardly show in detail that a thrombus may be regarded as equivalent to a resistance interpolated in the vessel in which it is seated, and that the mechanical effects of thrombosis are practically the same as those following an abnormal increase of resistance, whose highest degree, resulting from the complete occlusion of the vascular lumen, is here represented by the totally obstructive plug. But all thrombi, whether solid and firm or softened, have the effect of increasing the resistance, simply because the physiological integrity of the vessel wall or the lumen will, it is evident, never be re-established by the softening. With the effects of an increase of resistance on the circulation our previous discussion has made you perfectly conversant. As regards the veins in the first place you know that everything depends on the existence of compensating conditions, by whose aid the prejudicial effects of the abnormal resistance are neutralised. If channels be present capable of carrying off the blood from the vascular area in whose efferent vessels a resistance has been interpolated, we may certainly look upon this occurrence as a wholly insignificant accident. Should, on the contrary, efferent channels be wanting or insufficient, there will be on the peripheral side of the hindrance retardation of the stream, stagnation, crowding together of the blood-corpuscles, and œdema, all more or less intense in proportion to the interference with the efflux as compared with the afflux of blood. Should stagnation be extreme, diapedesis of the red blood-corpuscles may occur as a complication. If, lastly, the escape of blood be fully and permanently prevented, by the abnormal resistance, destruction of the affected organ is the inevitable result.

Applying these facts to the thrombosis of veins, we find numerous cases in which the occurrence is quite harmless, indeed indifferent to the circulation. So it is when some of the branches of a venous plexus or one of two companion veins has undergone thrombosis; the efflux is then in no wise interfered with even by a completely obstructive thrombus, to say nothing of a partially obstructive one. Where, on the other hand, coagulation occurs in veins having no roomy collaterals, we must be prepared for more serious consequences. Ascites is rarely absent in thrombosis of the portal vein, and the occlusion of the *v. femoralis* and its tributaries is followed by œdematous swelling, either of the ankle alone, or, if the thrombosis be extensive, of the entire leg or even thigh. Should we nevertheless come across a venous thrombosis, it may be of the obstructive variety, which, although the anatomical arrangement of the vessels be unfavorable, is unattended by prejudice to the circulation through the part concerned, two factors will have been influential in rendering this possible. In the first place the *tardiness* with which a thrombus always develops: from very small beginnings it attains such a size as to cause considerable narrowing or even complete occlusion of the venous lumen. When Litten and

Buchwald ligatured one of the *v. renales* in a rabbit or dog the invariable result was a high degree of atrophy of the organ, which after several days succeeded the primary swelling.* In contrast to this it is by no means uncommon to find in the dead human body a completely obstructive thrombosis of the *v. renalis* and its larger branches without any structural change in the kidney, indeed, without any condition of the urine *intra vitam* that might have pointed to a disturbance of the renal circulation. How is this to be explained? Very simply by the fact that in the latter case the occlusion of the vein came about slowly and gradually, so that sufficient time was allowed for the formation of new effluents. The less the quantity of blood escaping from the kidney through the *v. renalis* owing to the continuous growth of the thrombus the greater the amount flowing off through the capsular veins, &c., till finally the latter took up the whole of the blood supplied to the organ by the renal artery. In the second place the compensation of circulatory disturbances in venous thrombosis is uncommonly facilitated by a circumstance to whose importance I have already called attention, namely, that while coagulation of the blood in the capillary vessels occurs only after mortification of their walls, *i. e.* in necrosis of the part of the body implicated (in which case a restoration of the circulation would, of course, be out of the question), *the marantic thromboses and thromboses of compression, in short all the so-called thromboses of stagnation never extend to the capillaries, and are never propagated through them.* It is obvious that the maintenance of the smallest vessels in a pervious condition is vastly more favorable to the *re-establishment* of a free circulation than is the immediate compensation of the circulatory disturbance caused by the thrombus. For even in those cases where all the consequences of marked stagnation have prevailed for a long period, it is thus rendered possible for the venous channels which have meanwhile enlarged or have been newly formed at last to effect the removal of the venous blood. The œdema is then seen to decrease, the extremity reassumes its natural size and colour, results which may be materially furthered by the canalisation of the thrombus, should this happen to occur.

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* Litten und Buchwald, 'Virch. A.,' lxvi, p. 145.

The mechanical effects of simple venous thrombosis are generally those arising from stagnation, and when other signs appear in a part in whose veins thrombosis has taken place, these depend, as a rule, on some complication or other. Such being the fact, you will think it unnecessary to dwell any longer on the discussion of these consequences; for you are all able to account for the chemical constitution of the œdema in thrombosis, and can without difficulty infer the conditions in which the transudation will be colourless, or more or less tinged through admixture of blood-corpuscles.

In plugging of the arteries the point of critical importance is, as in venous thrombosis, the presence or absence of conditions favorable to compensation—is there beyond the plug, between it and the capillaries, a sufficiently large arterial anastomosis with the obstructed vessel? If there be, it is obvious that the plug has not the slightest pathological importance. The portion of the artery lying between the collaterals immediately above and below the plug will simply be excluded from the circulation; and should organisation of the clot ensue later on, the portion in question becomes transformed into a solid fibrous cord, or there arises a new, though narrowed, lumen. But thrombosis or embolism of an artery is harmless only when the distal anastomosis is roomy enough to accommodate the full amount of blood which would normally have passed through the vessel now occluded. For while small arterial vessels can, as you know, gain considerably in volume as the result of congestion, to do so, a certain time varying from a few minutes to a really long interval, it may be some days, is under all circumstances indispensable. Hence thrombosis of an artery is a much less unfavorable event than embolism, at least than completely obstructive embolism; for the partially obstructive variety must in this respect have precisely the same effect as slowly developing thrombosis. In the latter there is time enough for the small collaterals to dilate gradually, so that the affected part is never deprived of arterial blood, its supply being little less than normal. When, on the contrary, an embolus instantaneously and completely blocks the artery into which it has travelled, there must be an interval during which the supply of arterial blood to the part is much below normal, *i. e.* if the collaterals present are insufficient to accommodate the normal quantity of blood; in a word the part must become anæmic. It will depend, on the one hand, on the degree of anæmia and, on the other, on the special anatomical structure of the affected organs and their vessels, especially on their power of resistance or their vulnerability, whether any further pernicious effects ensue, and what these are.

Anæmia must also be the result when a terminal artery becomes the seat of a partially obstructive thrombus; while the formation of a completely obstructive plug must always have the effect familiar to you from our discussion of the consequences of occlusion of terminal arteries.* If the individual meeting with this accident lives long enough, there arises in advance of the plug either an uncomplicated necrosis or a necrosis associated with engorgement, and as a result of the latter hæmorrhagic infarction. Which of the two makes its appearance depends, as you will remember, either on the presence in the veins of valves capable of hindering the reflux of blood, or on the existence of other checks to engorgement by blood derived from the veins or capillaries. One point, however, I desire to emphasize, that if the artery be a terminal one, it is quite immaterial whether the obstruction be due to a local or a propagated thrombosis or to embolism. Compensatory conditions do not exist here, and thus the difference between thrombosis and embolism amounts only and solely to this, that in the former the effects are gradually developed, while in the latter they suddenly set in. The part in whose terminal artery a slowly growing thrombus establishes itself, receives less and less blood, till finally, when the plug has become totally obstructive, it is entirely robbed of its blood-supply and falls a prey to that necrosis which would have been its lot from the start had an embolus suddenly blocked the lumen of the artery. The only difference is that the engorgement and hæmorrhagic infarction may, for reasons readily understood, appear somewhat more frequently in front of an embolic obstruction than in front of a slowly developing thrombotic one.

In attempting to sum up the results of arterial obstruction in rules of general application, one must, in my opinion, restrict oneself to the foregoing. Even so, the great variety of characters assumed by the effects resulting from the formation of arterial plugs cannot have failed to strike you. At one time it is an event of no consequence, at another it is immediately fatal; here it produces anæmia, there necrosis; it is sometimes accompanied by hæmorrhage, sometimes not. Moreover, on calling in the experiences of pathology to your assistance, you are very soon confronted by occurrences that apparently cannot be brought within the limits of the principles set forth. Nothing is more common than to meet with obstructive emboli in the branches of the pulmonary artery without the parenchyma of the lung presenting the least deviation from the normal, while only too commonly do you see the foot become gangrenous in old people in consequence of thrombosis of the arteries of the leg. How is the former to be reconciled with the fact that the whole of the branches of the *a. pulmonalis* are typical terminal arteries, and the latter with the wealth of anastomoses and collaterals in the arterial system of the skin and muscles of the lower extremity? In order to clear up this apparent contradiction a most careful analysis of individual cases with respect to their various anatomical and physiological relations is required. The circumstance that such an analysis can be more perfectly carried out here than in the great majority of morbid processes is, in my opinion, the ground which, since Virchow laid the foundation of the whole doctrine, has made thrombosis and embolism a favourite study with pathologists. You yourselves will very soon be convinced that here, too, as so frequently happens in the natural sciences, the detailed examination of apparent exceptions to a fundamental law only leads to stronger confirmation of that law. Will you permit me, with this object, to examine with you some of the more frequently occurring and therefore more important cases in this domain of pathology?

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* Cohnheim, 'Untersuchungen über die embol. Processe,' Berlin, 1872.

Fixing our attention first of all on a region in which the arteries intercommunicate by more or less ample anastomoses, we find as a matter of fact that, in exact accordance with our preconceived notions, embolism of the arteries of the muscles and skin, as well as of the acinous glands and other localities, is unattended by any impairment whatever of nutrition and function in the part affected. The same holds good of isolated plugs in the intestinal arteries, and is no less true of the obstruction of any one of the vessels forming the circle of Willis. The circulation through the area in which the plug has become fixed is not even momentarily disturbed in these cases. But the fact that the collaterals have here an approximately equal calibre harmonises eminently with this result. Advance a step, however, take instead of a single muscle an entire extremity, or instead of a single loop the entire of the small intestine, and the conditions are at once altered. For the arteries entering an extremity are of very unequal calibre; besides the principal artery there are several others of much smaller dimensions: and while the small intestine is supplied by many *rami duodenales* derived from the *a. pancreatico-duodenalis* and by *rami colici* given off by the *a. mesenterica inferior* in addition to its chief afferent, the *a. mesenterica superior,* these are very far from comparable to the last mentioned in point of size. If now in such a territory the principal artery becomes occluded by an embolus, the law previously referred to asserts its sway, and a certain period must elapse before the remaining arteries can become sufficiently capacious to convey an adequate quantity of blood into the extremity or intestine. If mere relaxation of their tonic contraction were all that were required the anæmia would soon be at an end; but it is by no means all. With regard to the intestine Litten* has demonstrated directly that the pressure under which the blood normally flows in the arteries is, after closure of the *a. mesenterica superior,* not even approximately capable of supplying the customary and necessary amount of blood to the small intestine through the above-mentioned collateral branches. Moreover, the rapid fall in the temperature of a leg in whose *a. femoralis* an embolus has been arrested leaves not the slightest doubt that the quantity of arterial blood now received by the extremity has fallen considerably below its former value. In the lower extremity in man compensation takes place only slowly and gradually, in the course of some days, through progressive increase in the volume of the collateral arteries. The leg, which was at first quite numb and movable with difficulty, paretic, regains its warmth, sensibility, and muscular power, and not till then are the detrimental effects of the embolism compensated. Thus, despite the presence here of arterial collaterals beyond the seat of obstruction, several days are required for the removal of the circulatory disturbance. In the case of the small intestine, however, affairs take a much worse turn. For here a second factor has to be considered, namely, the great susceptibility of the organ and its vessels to injury from insufficient blood-supply. If the circulation through the intestinal vessels cease or be greatly diminished even for a few hours, it may happen that its re-establishment will be no longer possible. But even should it be restored, the nutrition of the walls of the intestine has generally suffered so much by reason of the ischæmia, that the time when gangrene might have been averted is already passed. It is therefore at once apparent that in embolism of the *a. mesenterica* the intestine is not secured against necrosis by the existence of the oft-mentioned collaterals. I may add that this necrosis is associated as a rule with hæmorrhagic infarction. Lastly, in an area abundantly provided with collaterals the formation of plugs in arteries may be quite as fatal should several, or still more, should all the afferent vessels be simultaneously affected, for it is obvious that a collateral which has itself become impervious is worthless for purposes of compensation. If, for example, the *a. tibialis antica* and *postica*, and perhaps some of their larger branches, be obstructed in the leg, this is at least as, if not more, detrimental to the circulation through the foot than would be the occlusion of the *iliaca externa* to the blood-supply of the entire extremity. A simultaneous obstruction of the arteries just mentioned has often been observed, and an extensive thrombosis in this arterial area in consequence of sclerotic and atheromatous changes in the intima is far from uncommon. Such an arterial thrombosis, when arising in an individual whose general circulation is feeble, *e. g.* in old men with fatty heart or any severe general disturbance, will be still more likely to weaken the circulation in the leg so as to disturb its nutrition. It was this complication I had in mind when saying that complete gangrene is often evoked by coagulation in the arteries of the leg, although arterial anastomoses are not wanting there.

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* Litten, 'Virch. A.,' lxiii, p. 289.

On the other hand, there exist in the organism a multitude of vascular areas with typical terminal arteries, which often enough become the seats of plugs; for example, the pulmonary artery with its branches, the *a. renalis* and *lienalis*, with the branches in the interior of the organs supplied by them, the coronary arteries of the heart, the *a. centralis retinæ* and Heubner's* so-called basal territory of branch arteries beyond the circle of Willis. We may also include here the *vena portæ* or rather its offsets within the liver, bearing in mind the course and arrangement of its branches. Now, what are the consequences of thrombosis in these vessels? We find here a series of facts in most perfect accordance with the requirements of the laws formerly laid down. Take, for instance, the immediately fatal effect of embolism in such of the terminal arteries as cannot, even for a short time, be withdrawn without danger from the circulation. When the main branches of the pulmonary artery of both sides are occluded by large plugs, death takes place instantaneously; in the first place because the interchange of gases in the lungs ceases at the moment embolism occurs, and in the second place because the supply of blood to the brain and medulla oblongata is of necessity cut off. In these suddenly fatal cases we have usually as a matter of fact to deal with embolic obstruction of the principal branches or at least of branches of the second order; nevertheless it is by no means impossible that the occlusion of smaller branches may be fatal if very large numbers of them are involved. Whoever has experimented much by injecting finely divided substances in suspension, *e. g.* vermilion, into the *v. jugularis*, has certainly suddenly lost many an animal in the midst of his experiment only and solely because too large a number of the minutest pulmonary arterioles have become occluded.

While in these cases the development of the other consequences of arterial obstruction is, of course, impossible, it is not so when the plug is seated in one of the other above-mentioned arteries or in one of their branches. The occlusion of a coronary artery—in case it does not prove fatal through the remarkable mechanism formerly discussed (p. 35)—leads to the destruction of the contractile substance of that portion of the heart which is fed by the affected artery, and afterwards to the formation there of so-called myocarditic indurations. After obstruction of the *a. basilaris*—clearly involving at the same time the occlusion of the branches given off within the compass of the thrombus and passing to the pons and the upper portion of the medulla—I saw quite recently a typical picture of acute bulbar paralysis; and the thrombosis or embolism of an artery of Heubner's basal territory is invariably followed by necrosis of that section of the brain supplied by the occluded vessel—a necrosis whose dimensions are exactly co-extensive with the ischæmia, and which may or may not be associated with hæmorrhage, a point I shall come to speak of afterwards. In like manner, necrosis of the spleen or kidney never fails to take place in the part of the organ whose artery is occluded by a thrombus; and in the retina the power of vision is extinguished at the moment when an embolus has become impacted in the central artery; after which the retina inevitably undergoes atrophy and destruction.

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* Heubner, 'Die luetischen Erkrankungen der Hirnarterien,' Leipsig, 1874.

But although these results thoroughly conform to our anticipations, we find a striking exception in the portal vein, previously referred to as one of the vessels which must be looked on as equivalent to a terminal artery. The branches of the *vena portæ* undergo absolutely no anastomoses; every *v. interlobularis* breaks up directly into the capillary network of the acinus. Should we not here expect the most typical hæmorrhagic infarction in every case of obstructive embolism of a portal branch, as well as in every thrombosis of the portal trunk itself? Yet nothing of the kind takes place. In the dog you may occlude a multitude of the larger branches of the portal vein by injecting coarsely powdered chromate of lead or wax-emulsion into a branch of the *v. mesenterica*, and yet no hæmorrhage or other change occurs in the liver. In pylethrombosis, whether this arise rapidly or slowly, you find ascites it is true, but in the liver, as a rule, nothing abnormal. There is, however, a good reason for this. For the capillaries of the hepatic acini are fed, as is well known, not merely by the portal vein but also by the hepatic artery; the capillaries of the latter unite to form small veins, which enter the *venæ interlobulares* as the so-called internal tributaries of the portal vein. If now the entrance of portal blood into one or more interlobular veins be for any reason prevented, there still remain the internal tributaries of the portal vein, the supply of blood through which is sufficient to avert necrosis of the organ, and all severe disturbance of the circulation in the hepatic lobules.[*]

Nor owing to the arrangement of the pulmonary vessels is a similar possibility of compensation altogether wanting in the lungs. For, as has lately been shown anew by a very painstaking investigation carried out in J. Arnold's laboratory,[*] the branches of the *a. pulmonalis* are connected with those of the bronchial arteries by a multitude of anastomoses, while the arteries distributed over the pleura and in the mediastinum also supply blood to the pulmonary vascular system. Nevertheless the fact that extensive obstruction of the pulmonary arterial system is attended by an immediately fatal effect proves clearly enough that all these connections are far from sufficient to permit the passage through the lungs of a quantity of blood sufficient for the maintenance of the circulation. It may well be asked, however—bearing in mind the absence of all arterial anastomoses between the branches of the pulmonary artery—whether it is not owing to these connections that plugs are so frequently met with in the smaller or larger offsets of the pulmonary without the least indication of disturbance of the circulation in front of them. This, it is true, is not always the case. Often enough we find most typical hæmorrhagic infarction in front of the obstruction in a branch of the pulmonary, a result in perfect accordance with the fatal effect of embolism of the main trunk. To make the whole affair appear still more enigmatical, it is quite common for a number of emboli to become lodged in a lung and the lung in front of them to be intact, and yet at the same time for one or more emboli to be found in it, in front of which infarction has occurred, although no sort of difference can be made out in the nature of the plugs. This cannot be attributed to the presence or absence of arterial anastomoses; for, I again repeat, such anastomoses are altogether absent from the ramifications of the *a. pulmonalis*. It is possible on the other hand that, as already indicated, the bronchial or mediastinal anastomoses lend their aid, although the inconstancy of the result does not say much for the efficacy of this means of compensation. The position of affairs becomes really comprehensible only when we take into consideration the peculiarities of the pulmonary circulation and of the parenchyma of the lung. In all other regions the resistance in the capillaries is, you will remember, so great that it cannot be overcome by the pressure of the blood flowing through the neighbouring capillaries; with the result that when arterial anastomoses are absent complete compensation in front of an abnormal resistance takes place first in the veins. The pulmonary capillaries on the contrary are considerably wider than those of the remainder of the body, and the resistance in them is by consequence less; so much so that the arterial pressure when reduced to a fourth of its normal value or still lower is sufficient to propel the blood through them into the veins. Add to this the constant changes in volume of the lung during respiration, to the action of which as aiding the circulation I have already repeatedly called your attention. In the vascular areas of the lungs, unlike those of all the other organs, the conjunction of these two circumstances makes it possible for the capillaries whose afferent vessels are occluded to receive blood from neighbouring capillaries whose vessels are pervious. The quantity cannot, it is true, be large, and the inflowing stream must be slow and feeble. But though the deficiency is not covered so far as the function of respiration is concerned, this small quantity of slowly moving blood, together with whatever blood the bronchial anastomoses may contribute, suffices to maintain the integrity of the implicated pulmonary capillaries and veins; nor indeed has the pulmonary blood any further nutritive function in the lung, the bronchi, the connective tissue forming the larger septa, and the larger vessels receiving, as is well known, their *vasa nutritia* from the *a. bronchialis*. This being the mode in which the evil consequences of obstruction of the pulmonary arterial branches are so often averted, it will be understood that it is effective only so long as the task required of the capillary circulation is not too severe. If the capillary stream be too feeble, as for example in fatty degeneration of the right heart or other condition depressing the heart's work, or should abnormal resistances in the pulmonary veins oppose it, as happens in valvular lesions affecting the left side, these means of compensation may prove inadequate, and the result will be hæmorrhagic infaction. That the latter should be so constantly met with at the periphery of the lungs close under the pleura and so very rarely in the neighbourhood of the hilus or in the interior of the organ at all may be very readily explained. In occlusion of a peripheral arterial branch, the capillary area, which in embolism of a central branch would be situated at the base of the ischæmic region and could have aided in restoring the circulation, is wanting.*

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[*] Cohnheim und Litten, 'Virch. A.,' lvii, p. 153.

[†] Küttner, ibid., lxxiii, p. 476.

Let us now spend a moment in considering the hæmorrhages which so often complicate the necrosis occurring in front of an arterial plug. You are aware that we have here to do with hæmorrhage by diapedesis from the capillaries and smallest veins, and that the disorganisation of the vessel wall due to the temporary anæmia is the cause of this diapedesis. The mode in which the blood arrives in these vessels has been thoroughly discussed on a former occasion (p. 121). Two possibilities present themselves according as the blood-supply to the affected part has ceased altogether, or is still maintained, though inadequately, by the agency of minute collaterals. In the first case—when the occluded vessel is a terminal artery—a reflux of blood takes place from the neighbouring veins and the contiguous capillaries into the ischæmic area; in the second case blood is conveyed into it principally by the scanty arterial collaterals. The mechanism of each of these processes is very different in some respects; yet it leads to the same result in the end. For both have one feature in common, that the quantity of arterial blood supplied is utterly incapable of maintaining the normal nutrition and physiological integrity of the vessel walls and of the part itself.

In which of these ways a hæmorrhage met with in front of an arterial plug has arisen cannot well be made out from the interval elapsing between the occurrence of obstruction and the commencement of the hæmorrhage; for in both cases a certain time must pass before the hæmorrhage sets in, and of course a still longer period before it attains somewhat large dimensions. On the other hand, a retrograde engorgement is with great probability indicated whenever the compass of the hæmorrhage exactly corresponds with the venous branches. If the hæmorrhages following the obstruction of arteries be examined in this aspect, the conviction must, it seems to me, force itself on everyone that at least the large majority have originated in precisely the same way as does the hæmorrhage observed to occur in embolism of the frog's tongue, while the organ is examined microscopically. In the spleen, kidney, and lung, the hæmorrhagic infarction always occupies a kind of cone or wedge, whose base is directed outwards, and apex inwards; and the vein whose tributary area is the seat of infarction is always found at the apex. In the hæmorrhages frequently met with in the brain after embolism of arteries, this conical or wedge-like form will certainly be sought for in vain; here the effusion usually assumes a more globular or elliptical shape. It must not be forgotten, however, that the arrangement of the venous channels in the brain is very different from that in the spleen or kidney. And moreover an ischæmic portion of the brain, in marked contrast to these organs, loses consistence so rapidly when deprived of its arterial supply that the support from the tissues so necessary to the production of a proper infarct is here wanting. The circumstance that hæmorrhages as the result of embolism of the *iliaca externa* or *axillaris* are so far as I know extremely rare seems to me to tell with no little force in favour of the venous nature of embolic hæmorrhages. But however this may be, you will hardly expect the effusions arising in this way to be voluminous; for, on the one hand, they are nothing but the effects of a scanty collateral circulation, and, on the other hand, the feeble and tardy venous reflux may be held in check by any sort of obstacle, as will be evident without further explanation. When hæmorrhages of thrombotic origin are really copious, this is necessarily owing to the presence of complicating factors by which the resistances and thereby the tension on the venous side are increased, a point on which I laid special stress when treating of pulmonary infarctions. The lungs, however, are almost the only localities where you frequently come across infarcts that are pronouncedly hæmorrhagic; it is very different in the spleen and kidneys, where infarcts have often enough but small claim to this title. For the great bulk of splenic and renal infarcts are wont to be decidedly pale and faded, opaque and almost clay coloured. Only at the apex and lateral boundaries is there, as a rule, an intensely hæmorrhagic zone, whose width varies greatly, not only in different infarcts but in one and the same example. The tolerably sharp boundary-line separating the two regions has the most irregular form imaginable. As to the faded clay colour displayed by the infarct, this is due solely to the necrosis, decolouration having had no hand in its production; and the irregularity of the boundary-line towards the hæmorrhagic zone depends only and solely on the irregular advance of the hyperæmic engorgement and consecutive hæmorrhage.*

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* Cohnheim und Litten, 'Virch. A.,' lxv, p. 99.

The question of the importance to be attached to coagula in the heart may be dismissed in a few words. For evidently they can only prejudice its action when they are large enough to interfere with the passage of the blood. It is true of course that an auricular appendix completely filled by a thrombus cannot receive any blood; nevertheless the normal amount will arrive in the auricle from the veins, and pass thence to the ventricles. Only those thrombi by which the cardiac orifices are narrowed are of importance to the circulation through the heart; yet even with regard to these, I have already dwelt on the fact that, because of their softness, their power of producing stenosis is generally not related to their size.

In the capillaries too the case is very simple, for since capillary thrombosis does not occur except on necrosis of the affected vessels we need only consider the effect of capillary emboli. But you are here again on perfectly familiar ground. From a former discussion you learned that the interpolation of an abnormal resistance in a single capillary is a perfectly insignificant event so far as the circulation through the area is concerned. The obstruction of capillaries can become of importance to the circulation in a part only when not one or a few but a very large number are the seat of embolism.

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* These points have recently been more thoroughly dealt with by Weigert, 'Virch. A.,' lxx. p. 486, lxxii, p. 250, lxxix, p. 87, whose statements have been [illegible] rmed by Litten, 'Zeitschr. f. klin. Med.,' i, Hft. 1.

That this has ever been observed of ordinary emboli such as are torn off from typical thrombi, I regard as extremely improbable, but the multiple obstruction of capillaries by other means than by coagula arising *intra vitam*, may attain serious proportions.

But with respect to the mechanical effects which the obstruction of a vessel brings in its train, it is evidently quite immaterial whether the plug consists of solidified blood or of other indifferent substances. Indeed, many of the most certain facts in our possession as regards the consequences of vascular obstruction have been gathered by experiments in which the experimenter prudently abstained from using blood-thrombi as material, preferring some other body less liable to decomposition and putrefaction. But it is not only in experiment that perfectly foreign and heterogeneous matters enter the blood-stream and are borne off by it. An echinococcus which has established itself in the myocardium and gradually grown into the cavity of the heart may be torn away and transported, according to its seat, into a branch of the pulmonary or into a systemic artery, the effects being indistinguishable from those of ordinary embolism. The most interesting and, owing to its comparative frequency, most important occurrence of this kind is the entrance of liquid fat into the blood, and its dissemination through the vascular system.

Before liquid fat can reach the blood-stream, it must exist somewhere in the body in a free state, *i. e.* not included in cells, and under conditions which allow of its entrance into the blood-vessels. These conditions are found in all imaginable perfection when vessels are wounded and open vascular lumina present at the seat of free fat ;[*] and it was actually for a long time supposed that free oil could arrive in the circulation only by thus entering it directly. Recently, however, it has been shown experimentally by Wiener[†] in the

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[*] F. Busch, 'Virch. A.,' xxxv, p. 321.

[†] Wiener, 'Arch. f. exper. Path.,' xi, p. 275. Cf. also Bergmann, 'Zur Lehre von der Fettembolie. Habilitationsschr.,' Dorpat, 1863; 'Berl. klin. Wochenschr.,' 1873, No. 33; Riedel, 'D. Zeitschr. f. Chir.,' viii, p. 571; Flournoy, 'Contribution à l'étude de l'embolie graisseuse,' Thèse, Strasburg, 1878; Halm, 'Beiträge zur Lehre von der Fettembolie. Habilitationsschr.,'

Institute here that fluid fat may also be taken up by the lymphatics during the ordinary process of absorption and then conveyed to the blood, and that this takes place more certainly and rapidly the more easily accessible are the lymphatic absorbents and the shorter and more pervious the lymphatic channel between these and the *d. thoracicus.* On injecting animal or vegetable oil into the subcutaneous cellular tissue of a dog or rabbit, several days usually pass before you can count with certainty on the first fatty emboli in the lungs, nor can these be compared in point of number with the emboli which may be produced in a very much shorter time by injecting oil into the thoracic or abdominal cavity. You must, however, be particularly careful to employ none but perfectly pure neutral oil, for should a purulent or fibrino-purulent inflammation follow the injection, resorption at once ceases. Pathological experience of fatty embolism harmonises completely with the results of experiment. Its in some measure classical occasion is presented by ordinary features of bone; the shattering of the bone-marrow provides the free fat, and the rupture of some of the vessels secures the presence of open vascular lumina. Moreover, fatty embolism is induced, though of course much less commonly, by ruptures and contusions of the liver and by severe bruising of the skin and subcutaneous fat.* That both in the lower animals and in man fluid oil may sometimes gain access to the circulation through resorption by the lymphatics is proved by the fatty emboli which have occasionally been found in acute suppurations of soft parts rich in fat, *e. g.* in the endometritis of lying-in women and analogous processes. The fat-drops having thus entered the circulating blood are simply borne along by it in the direction of the stream till they become impacted in vessels which, owing to their size, they are unable to pass. These are usually capillaries or at most the smallest capillary arteries; in the larger arteries their passage may be somewhat delayed when the drops come into contact with the vessel wall. The lung, as might be expected from the place of origin of the embolism, is the typical seat

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München, 1876; Scriba, 'D. Zeitschr. f. Chir.,' xii, p. 118, where a complete list of the literature is also given.

* Jolly, 'Arch. f. Psych. u. Nervenkrankheiten,' xi, p. 201.

of the fatty plugs, and here the oil-drops form most delicate casts of the capillaries. Not that the whole of the capillary network of the alveolus is filled with oil; it is more common for droplets to be arrested just at the angles of division or union of the capillaries, and there are generally several of them in the same alveolus, separated from one another by capillary columns of stagnant blood. No subsequent change takes place in the vicinity of these fatty emboli, for the oil-drops have merely the mechanical effect of occluding the lumina of the vessels. On cautiously injecting a fine emulsion of olive oil into an artery of the rabbit's ear or a similar emulsion of cod-liver oil into the arteries of the frog's tongue you obtain chiefly capillary emboli; those oil-drops which at first were seated in arteries of small calibre being after a time pushed on into the capillaries. Nothing of an abnormal character is observable in the tongue or ear either immediately after the injection nor on the following or succeeding days—at least if the number of capillaries occluded by the oil-drops be not unusually large. For the innocuousness of fatty emboli when few in number is of course nowise incompatible with the fact that the obstruction of a multitude of capillaries by liquid fat is a severe if not fatal occurrence. The portion of the ear, all or a greater part of whose capillaries are occluded by oil, invariably perishes, and when after a comminuted fracture of the leg fat-drops become impacted in most of the capillaries of all the pulmonary lobes death will be occasioned just as readily as by the occlusion with common emboli of a very large number of arterial branches; in the latter case it is not even necessary for the coagula to arrive on the lungs simultaneously. Nevertheless, it would appear that fatty embolism only very rarely terminates fatally, and I cannot avoid the impression that the importance of this process has been considerably exaggerated by surgeons, who are rejoiced at finding some palpable anatomical lesion in many surprising or unexpected fatal cases. In the animals experimented on, among which the rabbit is not distinguished by any special power of resistance, I have repeatedly seen the pulmonary capillaries filled with oil to a really incredible extent after injection into one of the serous cavities, and yet at no time previously nor immediately prior to its being killed did the animal present the slightest abnormality of respiration, heart-beat, or blood-pressure, in short, it behaved in every respect as before the operation. Accordingly, it may be regarded as somewhat doubtful whether the paroxysms of slight or severe dyspnœa, occasionally observed in cases of fracture, are really to be referred to fatty embolism, and it is also questionable whether, when an individual dies within the first twenty-four hours after receiving a fracture, his death is to be attributed to the emboli which, it must be admitted, are almost never absent from the lungs of such persons. Certainly another possibility should be borne in mind, by which the entrance of free fat into the circulation may prove destructive to life. Since oil is anything but a compact substance of unalterable form it is very easy for smaller or larger drops to be liberated from the oily casts in the pulmonary capillaries, and to be borne along by the blood-stream from the lung into remote regions. In truth, after injecting oil into the thoracic cavity of an animal nothing is commoner than to find arborescent fat-drops in the small systemic vessels throughout the entire body. They are met with in the villi of the intestines and in the heart, in the skin and muscles; further, they may be very beautifully and easily demonstrated in the brain, and most strikingly, too, in the kidneys, where very frequently the vascular tufts of numbers of the glomeruli are actually filled like moulds with the glittering fat. It is on this dissemination of the fatty emboli from the lungs throughout the systemic vessels that many surgeons lay special stress; it may be that they descry in the extension of the vascular obstruction over the entire body an enhancement of the danger, or, like Scriba,* look upon the filling of the cerebral vessels with fat as an accident of a peculiarly menacing character. It cannot be denied that these theories sound very plausible, and in fact I should be prepared to accept them without the least hesitation, were it not that our oft-mentioned experimental results call for decided reserve before subscribing to them. For amongst the animals in which we have determined not only the occurrence of embolism in the lungs, but also the occlusion with large quantities of oil of numbers of cap[illegible] in all possible organs of the body, were not a few which before being killed presented not the slightest functional disturbance of any organ, or were to be distinguished in any way from perfectly healthy animals. Does not the thought suggest itself here that the oil-emboli being composed of a substance capable every instant of changing its place and form, act very dissimilarly to a true thrombus consisting of coagulated blood or even still coarser stable material, and may it not be that the oil proves destructive to life only when a considerable bulk of it is introduced into the circulation suddenly or in divided portions at very short intervals? The migration of the oil-plugs from the pulmonary into the aortic system has, as you will notice, another and very welcome side, for it serves to disencumber the lung, and is, moreover, one of the means of which the organism takes advantage to expel the oil from the circulation altogether. True, we are at present very far from being acquainted with all the ways that nature takes in removing the fluid fat from the blood, but at any rate she effects this so thoroughly that some three or four weeks after the oil-injection no trace of it is to be met with in the vessels. So much is certain, however,—a portion of it is excreted with the urine through the glomeruli.

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* See foot[illegible].

One would naturally suppose that similar results should follow when, instead of oil, air gains admission to the circulation. Yet from some experiments of Panum* it is apparently to be inferred that air-bubbles are not of so innocent a character as fat-drops; and it is by no means certain that necrosis or inflammation may not sometimes arise in the vicinity of air-emboli. In any case these results fall completely into the shade when compared with the mechanical effects that invariably attend the entrance of a large amount of air into the blood-vessels. Leaving pathological experiment out of consideration, it is easy to say when such entrance of air will take place; it will occur whenever air comes into contact with the interior of a vessel in which the pressure is less than the atmospheric pressure. Such a condition is presented, as is well known, only by the large veins in the neighbourhood of the heart. The blood of the *v. cava superior*, *v. anonymæ*, and *jugulares*, and next to these of the *v. subclaviæ* and *axil-*

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* Panum, 'Virch. A.,' xxv, p. 499.

lares is so near the heart that the resistance here may be put down at zero. The pressure prevailing in these vessels is then barely positive, and it becomes negative at each inspiration. Now, should one of these veins be cut or otherwise wounded, the danger of a rush of air into the aperture at once arises, and air may thus be conveyed to the heart. When the quantity of aspirated air is but small, the occurrence is not usually attended by any further consequences, and a dog into whose jugular as much as from eight to ten cubic centimetres of air has been forced readily withstands the operation. Rabbits, on the contrary, are far more susceptible; but dogs too and even horses quickly and irrecoverably succumb when a large amount of air has entered or been forced into the jugular; convulsions and the symptoms of severe dyspnœa leading up to the fatal termination. Individuals have more than once died on the operation table owing to incision of the jugular or axillary vein through an unfortunate movement of the knife.

Under these circumstances, you can yourselves judge how much attention this fatal event must always have excited amongst pathologists, and how many the theories that have been brought forward to explain it. The view according to which the obstruction of the pulmonary arteries with air is the cause of death has finally met with pretty general acceptance. Nevertheless, there are several facts which do not, so far as I see, harmonise with this interpretation. If a certain amount of air be suddenly introduced into the jugular vein of an animal, death, as already stated, ensues in a few seconds; on the other hand, a much larger quantity may be caused to enter the veins with impunity, provided we take the precaution of introducing it in small quantities at certain intervals. How is this compatible with the supposed occurrence of air-embolism? The air that has settled in the capillaries cannot, during the few minutes elapsing between the successive introductions, leave or become resorbed from these vessels so rapidly as that this could constitute an essential difference between the effects of sudden and intermittent entrance of air. The chief objection, however, to the theory of air-embolism is the fact that the anatomical regions in which air is met with in fatal cases are not those which this hypothesis would lead one to anticipate. True, some few air-bubbles are commonly found in the branches of the pulmonary artery. A portion, however, as noticed by the older observers, is seated in the systemic veins, and very commonly in the sinuses of the *dura mater;* while the great bulk of it invariably occupies the right auricle and ventricle, which are, as a rule, found considerably distended, it may be to twice or three times their normal size, and filled with a pale reddish froth. This accumulation of air in the right heart is, in fact, the sole cause of the fatal termination. Each contraction of the right ventricle compresses the elastic air instead of driving it onwards; and it is this, as was recently proved by Couty* in Vulpian's laboratory, that confers on the accident its fatal character. For the right heart being permanently filled with air, the entrance of blood from the systemic veins is, of course, impossible, and in consequence the pulmonary circulation, and then the entire aortic circulation, ceases. In this way the fatal effect of a sudden introduction of a large amount of air into the heart is very simply explained. In order to cause death the right ventricle must be completely filled with air; for isolated bubbles will be carried off by the blood-stream, and become innocuous by being arrested in isolated pulmonary vessels. But if you bear in mind that far more than half the pulmonary blood-vessels may be occluded without prejudice to the circulation as a whole, to say nothing of danger to life, you will find it conceivable that a quantity of air which, when it occupies the heart, can occasion the gravest disturbance, is far from sufficient for the production of threatening symptoms by obstructing the pulmonary arteries or capillaries. From all which you may conclude that true air-embolism does not in the least merit the bad reputation which it had long borne amongst physicians, and which, indeed, is still attributed to it by many. Perhaps it differs in no respect from embolism with other substances having a purely mechanical action. It is, in fact, very much more favorable than many other varieties, inasmuch as air-bubbles may disappear in a comparatively short time from the capillaries of the lung, being carried out of them or undergoing resorption.

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* Couty, 'Étude expér. sur l'entrée de l'air dans les veines et sur les gaz intravasculaires,' Paris, 1875.

Accordingly, it will be seen that we were quite justified in taking up the subjects of fatty- and air-embolism in connection with the mechanical effects exerted by thrombi and emboli on the vascular system. Once more let me repeat that all thrombi, whether solid and compact or softened, act as local abnormal resistances; but the influence of some of them is not limited to this. We even give a special name to those which act merely mechanically as local resistances; they are called benign, bland, or non-irritative. However long such a benign thrombus or embolus may be seated in a locality, no event of importance ever occurs in consequence, if we leave out of account the circulatory disturbances already so fully discussed. The very most that happens is a slight and gradual thickening of the wall of the vessel in which the thrombus is situated; this affects the intima and to a greater extent the adventitia and surrounding connective tissue. The thickening has, of course, no significance whatever, and is therefore nowise comparable to the changes called forth by so-called malignant or infective plugs. The type of these malignant plugs is a thrombus in a condition of puriform softening.

How great a difference is occasioned by the nature of a thrombus or embolus in the local effects attending it in any given case is very plainly taught by a simple experiment. You need only introduce plugs into the median arteries of both ears in the rabbit. That on the left side should consist of a minute portion of clean cork or of a little lump of charpie or paper, while on the right side a small particle of decomposed flesh should be inserted. You now have a full opportunity for comparative observation of the effects attending the two kinds of plugs. On the left side, where a vessel is occluded by a foreign body which is neither liable to decomposition nor exerts any chemical action on the neighbourhood, the ear behaves precisely like a normal one; and the only change which in the course of weeks may in some cases be developed is a small, circumscribed, reddish tumefaction surrounding the plug, which, when the latter has become properly encapsuled, finally disappears. And now contrast the right ear with this one. During the first twenty-four or thirty hours, or even longer, you cannot, it is true, perceive any difference as compared with the other ear. Then, however, reddening and swelling invariably set in around the particle of flesh. In the course of the ensuing five or six days these spread and increase steadily, and may occasionally involve even the entire organ. In the midst of the intensely red, hot, and swollen concha and in the immediate vicinity of the plug there is developed a greyish-yellow purulent focus of 1½—2 cm. in diameter, and the epidermis covering this is transformed into shreds of necrotic tissue. Later on the whole patch is separated, the result being a complete perforation of the concha and sometimes the loss of a still larger portion of the ear. The lesson so clearly taught by this experiment will, I think, be apparent, even though we have not yet occupied ourselves with the subject of inflammation. The plug of flesh undergoing putrid decomposition excites in its vicinity a severe inflammation, which terminates in abscess or even in necrosis; while the reaction set up by the plug of charpie or cork is, on the contrary, quite minimal.

Now, while the simple benign thrombi behave exactly like the latter kind of plug, there are in human pathology others which must be judged of after the analogy of the particle of putrefying flesh. To the latter class belong those emboli which have an uneven, jagged surface, act as rough, foreign bodies, and by their unyielding character inflict injury on the vessel wall. In this way pieces of calcified cardiac valves may, as you will hear later, give rise to solutions of continuity of the arterial wall and lead to the formation of aneurysms.[*] But undoubtedly we must include in this category all those plugs in the production of whose effects a material undergoing decomposition or colonies of bacteria co-operate.

The wall of the vessel within which the infective thrombus is seated is naturally the first structure affected. It is for this reason that yellow softening is associated as a rule with inflammation of the venous wall, with a true suppurative phlebitis. The wall of the vein is then thickened *in toto;* the sheath of the vessel acquires a bright red colour, and the redness may even be due to hæmorrhage. The *adventitia* and *media* also become hyperæmic, and reddish patches glimmer through the non-vascular *intima*. Soon, however, purulent infiltration of the venous wall occurs, at first in the immediate vicinity of the *vasa vasorum*, then between the media and intima. The latter is elevated here and there by exudation, and on inspecting the inner surface of the vessel one gets an impression as though it were covered with small yellow pustules. The loosening of the intima continues to progress; it becomes crumpled and thrown into longitudinal folds, and may finally be ruptured and separated in small or larger shreds. Long before this, however, the intima has lost its glistening appearance; it now looks dull and faded, and in the worst cases has changed its colour. When the inflammation spreads in an outward direction suppuration of the periphlebitic cellular tissue takes place; and it is possible, especially in many animals, for the entire vessel wall to be perforated, and a communication established between the puriform contents of the vein and the vicinity, giving rise to the condition known as venous fistula. The phlebitis, you will observe, is in these cases the effect of the yellow softening—a point to be specially borne in mind, since the relation may be the converse of this. For when yellow or putrid softening occurs in a vein in contact with an ichorous focus or the like, the first thing to become implicated in the process is the wall of the vein. It undergoes purulent inflammation; and this sets up thrombosis, or at any rate the puriform liquefaction of the thrombus. When the whole series of phenomena is already developed, when a complete thrombophlebitis, as it is called, is present, it may often enough be difficult to determine its starting-point. Yet a broad consideration of the relations in question will as a rule lead to a certain conclusion as to whether the puriform softening has preceded or followed the phlebitis. The first is undoubtedly the commoner occurrence; but no matter what the sequence of events may have been, the thrombosis and not the phlebitis determines in every case the whole course of the disease.

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[*] Ponfick, 'Virch. A.,' lviii, p. 528.

For the inflammation is usually local and confined to the venous wall and its immediate surroundings, and no further extension is to be feared except when the inflamed vein lies immediately beneath a serous membrane, like the pelvic veins under the peritoneum or a sinus of the *dura mater* under the pia. But a thrombus from which emboli may be torn off can display its pernicious effects in various remote regions. Should an embolus arrive in a terminal artery its mechanical effects as evidenced by necrosis will, it is true, always preponderate. For these are very rapidly evolved, while inflammation, as shown in the experiment already discussed, develops as a rule but slowly. On the other hand, malignant emboli are most pernicious in those regions precisely where the benign form is completely innocuous, *i. e.* in arteries with an adequate collateral circulation and in the capillaries, for here the circulation is absolutely undisturbed by the plug, and the development of inflammation is therefore unchecked. Typical inflammatory foci are now formed around the embolus, just as around an infective foreign body situated outside the vessels, and moreover the foci resemble those around a foreign body in invariably terminating in the formation of abscess. The rapidity with which these suppurating foci arise, and above all their size and extent, depends chiefly on the degree of malignancy and the size of the embolus. A plug which is not arrested till it reaches a capillary gives rise to a small miliary abscess, while around an embolus too voluminous to pass a large vessel in the liver or lung large abscesses are formed. These are the so-called metastatic abscesses, which have long been regarded as characteristic of suppurative phlebitis, and which have made this disease so justly dreaded. For the rest, it might be advisable to employ the expression metastatic *focus* rather than abscess to express in general terms the effects of the specific malignant emboli, for besides typical and quite unmistakable inflammations, hæmorrhages may under certain circumstances result from these emboli—hæmorrhages which have no connection whatever with the variety already described as due to the occlusion of terminal arteries. Under other circumstances necrosis may be the consequence, and this is not seated beyond the plug, as is the case when terminal arteries are occluded, but occupies its immediate neighbourhood surrounding it on every side. Moreover, several of these processes may sometimes be combined in a very remarkable manner; thus necrosis may supervene on inflammation, or both of these be complicated by hæmorrhage. I must, however, for your own sakes ask permission to defer to a later occasion the discussion of the question, how and through what minute processes these various effects originate.

The localities in which metastatic foci are to be met with may be inferred from the fundamental rules already educed. In *endocarditis ulcerosa*, when the valves of the right heart are affected, it will be in the pulmonary circulation, while if the left heart be the seat of the disease it will be in the systemic vessels that metastases will be discovered. In the vast majority of such cases we have to deal with small miliary foci, such as would result from capillary emboli, but their diminutive size is more than compensated for by their incredible numbers, as revealed by an anatomical examination of the various organs. They are present in the skin and muscles; in the heart as well as the bone-marrow; in the kidneys, spleen, and intestines; in the brain and its membranes; in the testicles, in the eyes, in short when the aortic or mitral valves are the seat of ulcerative endocarditis there is, in fact, no organ which may not at one time or another be found occupied either by punctiform hæmorrhages (so-called *petechiæ*) or by small greyish-yellow necrotic foci associated with inflammation. A minute whitish point in the centre of the petechia or miliary focus, apparent as a rule even to the naked eye, leads us to suspect that embolism has occurred, and by a carefully carried out microscopic examination there is usually no difficulty in discovering the characteristic colonies of micrococci seated in a capillary vessel.

On the other hand, metastatic foci due to thrombo-phlebitis will be situated in the lungs or in the liver, according as the systemic veins or the portal tributaries are affected by the disease. Yet metastases may be induced in the aortic system by material conveyed through the pulmonary veins. These foci vary extremely in point of size; amongst them are some whose dimensions are very small, miliary; yet many of them may be as large as a walnut or even a Borsdorf apple or more. In contradistinction to the infarcts in areas supplied by terminal arteries, these metastases have usually a globular or approximately globular form, so that when they reach the external surface of the lung or liver they come into contact with the serous covering, not by their broadest portion or e, like the infarcts, but by only a small segment of their circumference. A most favorable opportunity for determining the complete similarity of these foci with lobular pneumonias terminating in suppuration is often presented in the lungs. For it is far from uncommon to find around malignant emboli in one and the same lung firm grey or greyish-yellow patches of hepatisation, together with others in process of transition from yellow hepatisation to purulent softening, and again others which are nothing more or less than abscess-cavities filled with tenacious yellow pus. On the other hand, the intimate connection of the inflammatory processes leading to suppuration with necrosis may be almost always demonstrated in the liver, especially in foci of recent origin. The growth of the focus is irregular, owing to the implication of one acinus after another in the necrosis, the one earlier, the other later, the suppuration succeeding the necrosis. That colonies of bacteria are almost always found in these metastatic abscesses will not surprise you after what has already been stated.

Yet this factor at once leads us a step farther. If colonies of micrococci be actually present in the circulating blood, it is clear that they, like air-bubbles or fat-drops, may be carried along by the blood-stream, till they reach a vessel which does not permit their further passage. Now, with reference to the fat-drops, I formerly stated that many of them pass through the capillary system of the lung and so arrive in the loops of the glomeruli, &c. The same holds good naturally of the colonies of bacteria. These are indeed still more likely to establish themselves in the various organs, not merely because the material of which they are composed is extremely soft and pliable, but because fragments torn off from a larger mass embrace within themselves all the conditions for subsequent growth, so that they may after a time be very easily arrested somewhere or other. If you bear these facts in mind you will have no difficulty in understanding how it is that in thrombo-phlebitis of a systemic vein abscesses are developed not only in the lungs but occasionally in organs supplied by the aortic circulation.

But for the production of these foci a thrombo-phlebitis is not even necessary. For if I am correct in what has just been stated, the importance of the thrombo-phlebitis in these cases consists solely in its affording a soil for the development of multitudes of bacteria within the circulation. Hence it follows that when in any other part of the organism a soil favorable to this development is presented, from which at the same time it is possible for bacteria to enter the blood-channels, metastatic foci may originate even without the intercurrence of a puriform thrombosis. And this is not a mere matter of inference, but has been repeatedly the subject of direct observation. Thus Weigert has seen several cases, some of them in Breslau and others in the institute here, in which he was able to determine that bacteria had penetrated from a suppurating wound into the neighbouring veins. On the internal surface of the wall of the veins there was no thrombosis, but merely a delicate dull bloom consisting wholly of bacteria. The lungs were free from abscesses, while the characteristic foci were present in the myocardium, liver, and kidneys. The liver, owing to the marked slowness of the blood-stream through it, is the favourite seat of these bacterial metastases. In fact after injuries or wounds hepatic abscess is so frequently found associated with abscess of the lung, that even subsequently to the establishment of the doctrine of embolism, not a few theories (some of them of a really remarkable character) were suggested to explain their origin. Now that we have become familiar with the pathogenic importance of the schizomycetes we can dispense with these peculiar theories, the more so as the liver is by no means the only organ in which the foci under discussion occur. They are also found in the myocardium, in the spleen and kidneys, in the brain and some other localities; and it is not unlikely that the inflammation of the intermuscular cellular structures and suppurations in joints, which are sometimes met with in conjunction with metastatic abscesses of the lungs, are attributable to the conveyance of bacteria to these regions.

The last part of our discussion has, however, carried us far into the domain of those highly important morbid processes, which in surgery have been long classed together under the name, purulent intoxication, pyæmia. Were we now to proceed further in this direction, and to examine, for example, into [illegible] nding the presence in the blood of the

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dissolved products of decomposition, such as must necessarily attend every thrombo-phlebitis, we should be wandering very widely from the task which we set ourselves in this lecture. The time has arrived when we may properly resume the thread of our discourse at the point where we let it drop, and continue the discussion of the influence exerted on the circulation by changes in the condition of the vessel wall. But though the connection of the latter portions of this lecture with our main purpose has perhaps almost escaped you, we were quite justified in dealing with the subject in this connection. For pyæmia was the point from which Virchow started when creating the whole doctrine of thrombosis and embolism, and it is the mechanical theory of the morbid processes in pyæmia that constitutes the most brilliant result crowning this doctrine.

Before concluding the chapter on thrombosis it seems desirable to touch on a side of the question which, it must be admitted, up to the present possesses a greater theoretical than practical interest. In the cases of thrombosis on which the foregoing discussion was based, the factor determining coagulation was always, as you will of course remember, the abolition of the specific action exerted by the vessel wall or rather by the endothelium. The latter, you are aware, has the property of maintaining the vitality of the colourless blood-corpuscles so as to avert as far as possible the danger which would arise from the formation of free fibrin-ferment, while it neutralises the influence of any ferment which may yet chance to be produced. But however eminent the services usually rendered by this enigmatical capacity of the vessel wall, it has, as I mentioned in our introductory observations, its quantitative limits, so that when from some cause or other large quantities of free ferment suddenly appear in the circulating blood, the vessel wall, though physiological and perfectly intact, does not prevent coagulation. This is a simple inference from Schmidt's doctrines, but for this very reason an experimental examination of the inference is the more to be desired, for in this way we may obtain important confirmation of the doctrines themselves. A. Schmidt, with an energy peculiarly his own, has undertaken this investigagation, which has been carried out very comprehensively. During the last few years a series of monographs has been issued from the physiological laboratory in Dorpat, which, although an occasional want of agreement in matters of detail is apparent, is well worth reading, and has enriched our knowledge in a way that claims our gratitude.* The results are, however, too numerous to allow of their communication *in extenso.*

The line of investigation pursued by all the researches in Dorpat is mainly the study of the condition and action of free fibrin-ferment in the circulating blood. In order to effect the introduction of a large quantity of ferment, A. Köhler took advantage of a fact discovered by Schmidt, namely, that during coagulation a considerable amount of fibrin-ferment is set free in the blood, so that blood in which coagulation has already taken place is rich in this substance. Such blood when introduced into the vessels of a living animal excites there an exquisite and extensive coagulation—as Köhler found even in his earliest experiments. This really most astonishing result may be most easily demonstrated on a strong rabbit. Ten to twelve cubic centimetres of blood are taken from an artery and allowed to clot into a solid cake; as soon as drops of serum commence to appear on the surface, the clot is cut up and the liquid expressed through a linen cloth. The blood thus obtained is filtered, and about 5—6 c.c. are slowly and cautiously injected into the *v. jugularis* of the animal from which it was withdrawn. As a rule, before the last drops have been injected there suddenly arises the characteristic opisthotonos; the pupils dilate widely; the animal, gasping for air, makes painful movements with mouth and nose; the heart labours powerfully, forcibly shaking the wall of the thorax—in short, we have the well-known and unmistakable picture of fatal pulmonary embolism. On rapidly opening the thorax as soon as the cornea has become insensible, and paralysis of all the muscles has announced the animal's death, you find the right heart, which still pulsates, full of tenacious matted clots, and all the branches of the pulmonary arteries of both lungs packed full of beautiful red thrombi, which may be followed as far as the smallest branches into which the scissors will pass. The left heart sometimes contains small clots, while the blood collected from the remainder of the vascular system is now conspicuous by the slowness and difficulty with which it coagulates. The experiment may be varied in many ways, *e. g.* by injecting the expressed blood into a mesenteric vein, or into the carotid in the direction of the aorta. By adopting the latter method you obtain a fatal thrombosis of the left heart and aorta, while by resorting to the former you produce a thrombosis of the *vena portæ*, which in rabbits is quite as destructive as cardiac thrombosis. But there is no essential change in the results of the experiment. It should be remarked, however, that the features presented by experiments of this kind are very far from constant. Thrombosis occasionally fails to set in, more especially in dogs, less often in cats and rabbits; but even in these cases the blood is less coagulable than before, and remains so for several hours.

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* Armin Köhler, 'Ueber Thrombose und Transfusion, Eiter- und septische-Infection und deren Beziehung zum Fibrinferment,' I.-D. Dorpat, 1877; Edelberg, 'Arch. für exper. Path.,' xii, p. 283; Birk, 'Das Fibrinferment im lebenden Organismus,' I.-D. Dorpat, 1880; Sachssendahl, 'Ueber gelöstes Hämoglobin im circulirenden Blut,' I.-D. Dorpat, 1880.

Another experiment, long ago devised by Naunyn and Francken,* forms a companion picture to this one of Köhler, and has acquired fresh interest in the light of the researches carried out at Dorpat. A few cubic centimetres of blood are defibrinated, repeatedly frozen and thawed, heated to 60°, or treated by passing induction currents through the liquid till it becomes transparent; this transparent liquid is then injected into one of the veins or arteries of a cat or rabbit, when after a very short interval an extensive coagulation results. Naunyn has also repeatedly succeeded in procuring acute thrombosis in the vascular system by the infusion into some part of it of cholates or of ether; in other words, by causing a rapid solution of large numbers of corpuscles in the circulating blood; even the injection of pure dissolved hæmoglobin was attended with the same success. No satisfactory explanation of these experimental results, on the accuracy of which doubt has been unfairly cast, was offered by Naunyn. We now know that when blood passes from a frozen to a liquid condition, the transition is attended by the release of a considerable quantity of fibrin-ferment, and that dissolved hæmoglobin greatly enhances the efficacy of the latter. Finally, Edelberg has removed all remaining doubt as to the specific action of the fibrin-ferment by producing instantaneous, and in many cases fatal, coagulation by the use of more highly concentrated solutions of pure fibrin-ferment than had been employed by former unsuccessful experimenters.

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* Francken, 'Ein Beitrag zur Lehre von der Blutgerinnung im lebenden Organismus,' I.-D. Dorpat, 1870; Naunyn, 'Arch. f. exper. Path.,' I, p. 1; Ploss und Györgyai, ibid., II, p. 211.

These experiments may then be regarded as affording irrefutable proof that coagulation may take place in the living circulating blood even when the vessel wall, including the endothelium, is perfectly intact and physiological; and the only question open for discussion is—whether the prepared fibrin-ferment introduced into the blood is the sole cause of the thrombosis, or whether in consequence of the experiment described above many of the blood-corpuscles are not also dissolved and fibrin-ferment set free in the blood itself. This latter possibility is one which, in view of the considerable diminution of coagulability of the blood after injection, must certainly receive consideration. However this may be, a thrombus so originated must belong to the red variety since it is composed of the whole quantity of blood present in the affected vessel. In this respect it vividly recalls the thrombosis of stagnation of older authors, though as regards the conditions of their development the two processes have nothing whatever in common. To the pathologist, however, the question presents itself—does this mode of thrombus-formation, due to sudden overloading of the blood with fibrin-ferment, the vessel wall being uninjured, occur under natural conditions? Indeed Köhler had set this problem before him, and imagined he had cleared up or explained by his results a number of the weightiest and most complicated questions, such as putrid intoxication, septic and purulent infection, the dangers attending transfusion of blood from a different species; yet I cannot say that he has been so happy in his inferences as in the experiments themselves. The error underlying his deductions consists, so far as I see, in his attributing an important part to thrombosis of the capillary vessels; for since it is impossible to explore the capillaries with forceps and scissors, I am at a loss to understand how a thrombus occupying a capillary is to be diagnosed from an ordinary *post-mortem* clot. The notion of a capillary thrombosis due to ferment intoxication being accordingly somewhat fanciful, Köhler is still further from proving that the numerous hæmorrhagic, inflammatory, or necrotic foci characterising the above-mentioned processes have really any sort of causal connection with capillary thrombosis. Most of the Dorpat researches have traced out the history of pathological ferment-intoxication in other directions, especially with regard to its influence on bodily temperature. We shall meet with them again when considering the latter subject. But I am at present unable to perceive any gaps in the history of thrombosis as observed in morbid conditions that would oblige us to have recourse to the theory of ferment-intoxication in order to fill them up.

In conclusion, I may refer to a circumstance which is related, in a certain sense, to the question that has just occupied our attention. Amongst the exciting causes of thrombosis I mentioned contact of the blood with foreign bodies which have penetrated into the interior of the heart or vessels, and my justification for this was the fact that in the great majority of cases of this class contact of the blood with a portion of the vessel wall is prevented by the presence of the foreign body. But it is conceivable that a foreign body might remain in the midst of the circulating blood without at the same time touching the vessel wall. For example, when in a large dog a sound is introduced through the *v. jugularis* into the heart, it will of course be in contact with the wall at the spot where it is secured in the vessel, but it need not touch the inner surface of the auricle or ventricle. Under these circumstances when the blood is at the same time in contact with a foreign substance and with the perfectly normal endocardium, the nature of the subsequent events depends altogether on the character of the foreign body. If this be a completely indifferent substance having a perfectly smooth surface, as, for instance, a carefully smoothened, rounded off, and cleaned glass rod, it may lie there day after day, and no clots need be deposited upon it. On the other hand, if the rod be of iron or whalebone, or if a rough, uneven, or still more chemically different body be introduced, however carefully cleansed this may be, coagulation never fails to take place. In other words the effect depends solely on whether the foreign body does or does not exert a deleterious influence on the colourless corpuscles that approach it. In the latter case the blood continues perfectly fluid; in the former the endothelium, though intact, is unable to prevent the deposition on the foreign body of true thrombi, which are then of the white variety.

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* The celebrated researches of Virchow, most of which have been published in a collected form in his 'Gesammelte Abhandlungen,' pp. 219—732, form the foundation of the whole doctrine of thrombosis and embolism. A *résumé* of them has been given by the author in his 'Handbuch d. spec. Path.,' i, p. 156. Cf. in addition C. O. Weber, 'Handbuch,' i, p. 69; further, Billroth's 'Allg. Chirurgie;' Ule und Wagner, 'Allg. Path.;' Perls, 'Lehrbuch d. allg. Path. etc.'

CHAPTER V.

INFLAMMATION.

Arterio-sclerosis.—Fatty degeneration of the vessels.—Amyloid degeneration.—Molecular changes in the vessel walls.—Microscopic observation of the exposed mesentery and of a wound of the tongue, as well as of the frog's tongue after painting it with croton-oil, touching it with nitrate of silver, or after the temporary application of a ligature to its root.—The rabbit's ear similarly treated.—Explanation of the results on the hypothesis of molecular changes in the vessel walls.

Cardinal symptoms of inflammation.—Rubor.—Tumor.—*The lymph-stream in inflammation.—The blood-pressure in the vessels of an inflamed part.—Constitution of the inflammatory transudation.—The blood in inflammation.—The red blood-corpuscles in the exudation.—Exudations poor in cells.—Inflammation without* tumor.—*Manner of manifestation of the inflammatory* tumor.—Dolor.—Calor.—*Dependence of the latter on the quantity of blood circulating through the inflamed part.*—Functio læsa.—*Comparison with the local disturbances of the circulation.*

Critique of the neuro-humoral theory of inflammation.—Importance of the nerves in inflammation.—Critique of the cellular theory of inflammation.—The so-called progressive changes in inflamed tissue-cells.—Keratitis.—Elucidation of the hypothesis of a molecular change in the vessel walls.—Rejection of a theory of stomata.—Extravasation a process of infiltration.—The alteration in the wall probably a chemical one.—Possible co-operation of the nervous system.

Causes of inflammation.—Toxic inflammations.—Wounds.—Influence of schizomycetes.—Infective inflammations.—Contagium vivum.—*Biology of the contagium of* *anthrax.—Specific nature of pathogenic bacteria.—So-called rheumatic inflammations.*

Sthenic and asthenic inflammations.—Classification of inflammations according to the character of the exudation.—Acute exanthemata.—Serous inflammations.—Exudations in nephritis.—Inflammatory œdema.—Fibrinous inflammation.—Interstitial inflammations.—Purulent inflammation.—The poison producing suppuration.—The micrococci of sepsis.—Actinomyces.—Hæmorrhagic inflammation.—Mixed and transitional forms.—Catarrh.—Stages of inflammation.

Terminations.—Death.—Local necrosis.—Restitutio in integrum.—*Removal outwards of the exudation.—Inspissation of the exudation.—Progressive inflammation.—Secondary, metastatic, inflammations.*

Retrogressive and degenerative changes in the tissues during inflammation.—Weigert's primary lesions of the tissues.—Regenerative processes.—The formation of connective tissue by productive inflammation.—Fate of the pus-corpuscles in exudations.—Giant-cells.—Gluge's corpuscles.—Formation of blood-vessels.—Formation of vascular connective tissue.—Newly-formed tissue produced in excess.—Combination of regeneration with productive inflammation as exemplified in the healing of wounds, the repair of fractures, and in keratitis and peritonitis adhæsiva.—Chronic inflammation.—Causes of chronicity.—Varieties of chronic inflammation.—Forms assumed by the newly produced connective tissue.—Atrophy due to contraction.

The influence of other disturbances of the circulation and of changes in the constitution of the blood on the origin and course of inflammations.—Predisposition to inflammation.—Inheritance of infective inflammations.

When the walls of the smaller vessels have undergone such changes that they perish throughout their whole thickness, or when larger vessels are so altered that their innermost layers lose their vitality and living functional capacity, the blood coagulates in them—there arises, as we have seen, a thrombosis. This is evidently the highest conceivable degree of change of which the vessels are capable *intra vitam*. But it is no less evident that it is not the only possible kind of change; and before proceeding to examine into the manner in which alterations in the vessel walls influence the circulation, it will be necessary first of all to look about and see what other processes, impairing their physiological constitution, are met with in pathology. One group of these, including wounds, ruptures, in fact all *solutions of continuity* of the vessel walls will be minutely dealt with further on; many others—*aneurysms, varices,* and *stenoses; calcification of the tunica media* of arteries, *arterio-sclerosis* and *atheroma*—have been considered in previous lectures. To many of you, perhaps, it may have appeared remarkable that we should have placed all these processes under the one head of alteration of resistance, and have paid no attention to the fact that the structure and constitution of the vessel walls present very essential deviations from the normal. But though I am not of course at all disposed to deny this fact, we were justified in proceeding as we did, inasmuch as the structural changes in the vessel walls were of no importance for the circulation in these cases except *by virtue of their power of altering the resistance.* An artery which has become rigid from petrification of the media cannot of course dilate or contract, while at the same time the aid usually afforded to the circulation by the elasticity of the arterial wall then ceases to be rendered. But within these limits the circulatory disturbance, which may yet be very considerable, is strictly confined. Nor is it otherwise in arterio-sclerosis and atheroma. However much the vascular lumen may be narrowed by the thickening of the intima, however greatly the dilatation of the lumen through relaxation of tonus may be impeded, so long as the endothelium continues intact, no other consequence whatever can result to the circulation. The same consideration applies still more to the thickenings of the walls of the veins which are due to chronic endophlebitis; here indeed it applies with full force, if for no other reason, because the resulting prominences never become so considerable as do the knobs and plates in chronic endarteritis.

While these processes are by no means absent in vessels of small calibre, it is in the larger arteries that they are chiefly developed. In contrast to these—since it occurs in vessels of every kind and size, in the minutest perhaps more frequently than in the larger—is another pathological condition, namely, *fatty degeneration*. Numerous, very delicate, fatty patches, often perceptible to the naked eye, are very commonly met with in the intima of the aorta and other large vessels; fatty degeneration is nothing unusual in the muscularis of small arteries, and is still more frequently discovered in the adventitia of arteries and veins of fine calibre; but even in the walls of capillaries, *e. g.* in the brain and other localities, the occurrence of more or less large numbers of fat-droplets is far from rare. Although fatty degeneration of the vessels is so common an event, we can say but little of a positive character with regard to its significance. Many are the statements concerning it in the literature; and were we to judge solely from the cases for which fatty degeneration of the blood-vessels has been made responsible we might easily be tempted to concede it a large place in our discussions. The majority of such statements are, however, far from proved. The assertion that the contractile power and tonus of a fatty muscular coat are diminished is indeed plausible; and, similarly, there is much in favour of the assumption that vessels when fattily degenerated have suffered a loss of cohesion, and are therefore more fragile and easily torn. Of the last-mentioned factor I shall have to speak more at length in connection with ruptures of the vessels. But with respect to other circulatory disturbances in vessels whose walls are the seat of fatty metamorphosis, we know at any rate nothing of a certain nature.

There is a greater degree of probability in favour of the assumption that such disturbance occurs in another pathological process which affects by predilection the small arteries and less often the capillaries and veins, namely, *amyloid* or *lardaceous degeneration*. This is to be inferred at least from the fact that, as will be explained more in detail when we come to treat of the pathology of this condition, the metabolism suffers in the cells and tissues which are supplied by vessels that have undergone amyloid degeneration; and the inference is borne out by some very definite signs which point to an abnormal exchange of fluids through the diseased ry walls. I have in mind the glomeruli of the kidney, which when thus degenerated allow considerable quantities of albumen to percolate through them, as well as the severe and uncontrollable watery evacuations, diarrhœas, accompanying lardaceous degeneration of the vessels of the villi. Many have held that by the amyloid degeneration abnormal resistances are interpolated in the circulation, or even that the degenerated vessels may become completely impervious to blood. The latter possibility can be entertained, if at all, only in the most severe form of the disease; and with regard to the nature of the supposed circulatory disturbance, *i. e.* in what respect the blood-stream through lardaceous vessels deviates from the normal, we are wholly in the dark. Moreover, we shall probably long remain so, for the simple reason that, so far as I know, amyloid degeneration has been observed in our domestic animals only in very rare cases, and then as a mere accidental *post-mortem* appearance, for which no definite aggregate of symptoms *intra vitam* had prepared us.

This is all we know of the anatomical changes of the vessel walls, such changes as are discoverable by the scalpel and forceps, or by the microscope. But it seems to me it would be nothing short of an insult to common sense were we to confine all possible alterations in the constitution of the vessel walls within these limits; were we, in other words, to pronounce all vessels to be healthy, normal, which are neither sclerosed nor fattily degenerated, nor in the amyloid condition. If it is impossible to judge from the appearance of an endothelial cell, or even of an entire capillary, whether it is living or dead, how, I ask, will you venture to decide from its optical characters alone whether the constitution of a vessel is normal? How can a microscopical examination exclude a possible chemical or physical, so to speak, *molecular* deviation from the normal.

In fact, a moment's consideration will show that such molecular alterations in the condition and constitution of the vessel walls *must* take place. This conclusion is, it seems to me, inevitable, inasmuch as in the blood-vessels, like all the tissues and organs of the animal body, *the transition from intact physiological life to death is only in exceptional cases sudden, and is, as a rule, sl*[illegible] *gradual.* If you withdraw a loop of intestine fro[illegible]lomen of a rabbit and expose it to the air, it, together with its vessels ultimately perishes, but death is far from instantaneous; rather a comparatively long interval must elapse before this point is reached, and during it the disorganisation of the tissues and vessels progresses little by little till they finally die. If you cut off the circulating blood from a part and its vessels, necrosis sets in; but here, again, as you know, a very considerable period passes during which the tissues, *in specie* the vessel walls, become gradually disorganised. At a temperature of from 36°—38° C. the life and function of the blood-vessels are regular and normal, at one of say 60° C. they are certainly destroyed. Now, if you expose a vascular part to a temperature somewhere between these extremes, though it does not die, the heat is not without its effect on the constitution of the vessel walls. Lastly, in order to kill a part with its vessels by the action of sulphuric acid, the latter must have a certain concentration; a weaker solution is, however, far from innocuous although it does not instantaneously destroy the vitality of the vessel walls. These examples will, I think, explain the drift of my thoughts, for they show that alterations in the constitution of the vessel walls, for which the term *molecular* just now appears to be the most suitable designation, are called forth by a number of influences of the most different kinds. But if such alterations occur we are justified in asking—*what effect have they upon the circulation?*

Yet, however natural this question, it is impossible to answer it *a priori*; the direct observation of appropriate cases is necessary, and it will be best, with this end in view, to have recourse to express experiment. This may be carried out without any difficulty. You need only expose the vessels of a part to the air by removing its protective coverings; when if you have selected a transparent tissue, there is nothing to hinder microscopic observation. The simplest method is to draw out the intestine of a curarised frog through a laterally placed opening in the abdominal wall, and to bring the mesentery under the microscope, after having carefully spread on a slide adapted to the purpose. Or you may wound ary surface of the frog's tongue by removing the a cut of the scissors, carried parallel to the surface; a number of larger and smaller vessels will thus be exposed in the base of the wound. No further violence should be used after this; on the contrary, the more carefully you protect the preparation from all disturbing accidents, as contamination by blood, stretching or loss of moisture, the more regularly will a succession of appearances be developed, which are well calculated to fully engross your attention.*

The first thing you notice in the exposed vessels is a *dilatation* which occurs chiefly in the arteries, then in the veins, and least of all in the capillaries. With the dilatation which is gradually developed, but which during the space of fifteen to twenty minutes has usually attained considerable proportions (often exceeding twice the original diameter) there immediately sets in in the mesentery an *acceleration of the blood-stream*, most striking again in the arteries, but very apparent in the veins and capillaries also. Yet this acceleration never lasts long; after half an hour or an hour, or sometimes after a shorter or longer interval, it invariably gives place to a decided *retardation*, the velocity of the stream falling more or less below the normal standard, and so continuing as long as the vessels occupy their exposed situation. Such is the course of events in the mesentery experiment, in which not only the vessels of the mesentery but their terminal ramifications in the intestine are laid bare. In the wound of the tongue, on the other hand, the acceleration is often altogether absent; and *from the first there is associated with the dilatation a retardation of the stream*, which increases as the dilation increases. This is the case at least when a number of larger branches are exposed in the wound, but not their finer ramifications. Should the latter also be laid bare, a temporary acceleration precedes the slowing of the blood-stream, which never fails finally to set in in the exposed vessels.

This stage having been reached, the vessels are seen to be all of them very wide; a multitude of capillaries which were formerly hardly perceptible can now be clearly distinguished; pulsation is unusually conspicuous on into the finest ramifications of the arteries; while the flow is everywhere slower than normal, so that the individual corpuscles may easily be recognised not only in the capillaries but also in the veins, and during diastole even in the arteries. In consequence of the tardy forward movement the corpuscles accumulate in large numbers in the capillaries, so that the latter appear redder than usual, and therefore fuller, more voluminous; yet their cross-section, as just stated, is only very inconsiderably enlarged. But it is the veins rather than the capillaries that attract the notice of the observer; for slowly and gradually there is developed in them an extremely characteristic condition; *the originally plasmatic zone becomes filled with innumerable colourless corpuscles.* The plasmatic zone of the veins, you will remember, is always occupied by scattered colourless blood-corpuscles, which, owing to their globular form and low specific gravity, are driven into the periphery of the stream, and whose adhesiveness makes it difficult for them to escape from the wall once they have come into contact with it.* It is obvious that this difficulty will be enhanced in proportion to the slowness of the blood-stream; and thus it is not surprising that a gradual accumulation of large numbers of colourless corpuscles should take place in the peripheral zone, and here come to be *comparatively* motionless. For that a state of absolute rest, an actual standstill is out of the question, I need hardly mention expressly; the colourless cells of the plasmatic layer remain stationary at most for a time, they then advance a little, and perhaps make another short halt, and so on. Yet this does not lessen the striking contrast presented by the central column of red blood-corpuscles, flowing on in an uninterrupted stream of uniform velocity, and the peripheral layer of resting colourless cells; the internal surface of the vein appears paved with a single but unbroken layer of colourless corpuscles without the interposition at any time of a single red one. It is the separation of the white from the red corpuscles that gives the venous stream in these cases that characteristic appearance, anything analogous to which you will look for in vain in the other vessels. For in the capillaries, although large numbers of colourless blood-corpuscles adhere to the walls, there is always an admixture of red cells, or rather these are very decidedly in the majority. Lastly, in the arteries there is seen during diastole, almost at the moment of exit of the wave, a number of colourless blood-corpuscles rolling straight towards the periphery; yet these are always swept into the stream at the next systole, so that the development of a resting peripheral layer is here altogether out of the question.

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* A. Waller, 'Philosoph. Magaz.,' 1[illegible] pp. 271, 378; Cohnheim, 'Virch. A.,' xl, p. 1, xlv, p. 333.

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* Donders, 'Physiologie,' über. von Theile, 2nd ed., p. 135; E. Hering, akad. Stzgsb.,' lvii, Abthlg. 2, Februarheft, 1868; Sklarewsky, [illegible],' i, pp. 603, 657.

But the eye of the observer hardly has time to catch all the details of the picture before it is fettered by a very unexpected occurrence. Usually it is a vein with the typical peripheral arrangement of the white corpuscles, but sometimes a capillary, that first displays the phenomenon. A pointed projection is seen on the external contour of the vessel wall; it pushes itself further outwards, increases in thickness, and the pointed projection is transformed into a colourless rounded hump; this grows longer and thicker, throws out fresh points, and gradually withdraws itself from the vessel wall, with which at last it is connected only by a long thin pedicle. Finally this also detaches itself, and now there lies outside the vessel a colourless, faintly glittering, contractile corpuscle with a few short processes and one long one, of the size of a white blood-cell, and having one or more nuclei, in a word, *a colourless blood-corpuscle*. While this is taking place at one spot, the same process has been carried on in other portions of the veins and capillaries. Quite a large number of white blood-cells have betaken themselves to the exterior of the vessels, and these are constantly followed by fresh ones, whose place in the peripheral layer is immediately occupied by others. Like every stage of the entire process on from the moment of exposure, these phenomena may develop either rapidly or slowly; at one time the earliest *emigration* very quickly succeeds the pavementing; at another an hour or more may pass without anything happening to draw attention to the contour of a single vein or capillary. In any case the final result, after six or eight or more hours have elapsed, will be the enclosure of all the veins, small and large, of the mesentery or wound of the tongue with several layers of colourless blood-corpuscles. These fence in the veins, in the interior of which the previously described conditions continue, namely, the peripheral arrangement of the colourless cells and the central unbroken flow of red blood-corpuscles. Nothing analogous has occurred in connection with the arteries, *their contour has remained smooth as before*, nor can a solitary corpuscle, red or white, be discovered on their outer surfaces, except of course such as may have reached them from the neighbouring veins. On the other hand, the capillaries take, as already mentioned, a very active part in the process, yet these and the capillary veins differ remarkably from the veins proper in that not merely *colourless* but *red* corpuscles emigrate from them. This result is completely in harmony with the condition of the stream in these vessels, for I have already called your attention to the fact that in the veins only white corpuscles, in the capillaries both varieties, are in contact with the vessel wall, so that whether a preponderance of white or of red corpuscles passes out of a given capillary depends solely on the numerical relations of the cells accumulated in its interior.

Keeping pace with this *exodus*, *emigration*, or, as it is also called, *extravasation* of corpuscular elements there occurs an increased transudation of fluid, in consequence of which the meshes of the mesentery, or the tissues of the tongue, are infiltrated and swell. But this is not all. The extravasated colourless corpuscles distribute themselves, in proportion as their numbers increase, over a larger area, forsaking the neighbourhood of the vessels from which they were derived. The tissues become more and more densely packed with them, while the red cells, which have not the power of independent locomotion, remain seated in the vicinity of their capillaries, yet these also may be carried off by the stream of transudation. Soon a moment must arrive when the products of exudation and transudation can no longer be accommodated in the tissues. They now gain the free surface of the mesentery, and should the transuded fluid coagulate, as is the rule here, the final result of the processes just described will be *the deposition on the mesentery*, as well as on the intestine, *of a fibrinous pseudo-membrane, densely packed with colourless blood-corpuscles, and interspersed with isolated red cells.*

The appearances are essentially the same after painting the smooth surface of the frog's tongue with *croton-oil*. Of course it is absolutely necessary to employ the croton-oil in extreme dilution—about one part to forty or fifty of olive oil—and even then to allow the mixture to act only a very short time. For if you do not soon wipe off the oil, or still more if you make use of a concentrated solution, you at once get an intense corrosive action, as evidenced by the *formation of thrombi* in the larger vessels, and the occurrence of complete *stasis* in some of the capillaries, more especially in the superficial ones. The weak solution, on the other hand, provokes *an enormous dilatation of all the vessels,* which at first is accompanied by *a very great acceleration of the blood-stream.* After a time, however, the velocity commences to diminish in the dilated vessels, and is converted into a pronounced retardation of the entire circulation through the tongue. With the retardation there is simultaneously developed the *peripheral arrangement of the colourless blood-corpuscles in the veins,* and the accumulation of blood-corpuscles in the capillaries, which is so extreme as to result in the actual stagnation of the red cells in such of the latter as are superficially situated. And now it will not be long before extravasation from some of the capillaries and veins begins. As might be expected, the veins supply only colourless corpuscles; the capillaries whose blood is becoming stagnant almost exclusively red, while from those capillaries in which the flow, though retarded, is still sustained, coloured and uncoloured cells pass out together, at one point more colourless, at another more red, and these may even collect into small clumps outside the vessels. At the same time the swelling of the tongue gradually increases, it becomes intensely reddened; a multitude of small punctiform hæmorrhages are already apparent even to the naked eye, while microscopic examination reveals a no less dense accumulation of colourless corpuscles throughout its tissues.*

The development of this process is still more evident and more easily observable when only a portion of the tongue, and not the entire organ, is corroded. The action of the caustic shades off and becomes gradually feebler towards the periphery, so that, by passing from the circumference to the centre of the injured part, one has an opportunity of examining side by side the whole of the processes, which otherwise are observed to develop in succession. On microscopic examination of the frog's tongue, a circumscribed portion of which has been touched with nitrate of silver or other caustic on the previous day, you find the vicinity of the part to which the caustic has been applied swollen, and presenting a number of almost concentric zones. At the periphery you come upon a perfectly normal circulation, then upon a zone of dilated vessels, in which the flow is retarded, but whose contour is smooth; next upon another zone of dilated vessels, from which abundant extravasation is taking place—an extravasation, as invariably happens, of colourless blood-corpuscles from the capillaries and veins, and of red cells from the capillaries. Then follows still another zone, in which the flow is excessively retarded and the capillaries densely packed with red corpuscles almost at rest: it is here you meet with the most copious diapedesis of red corpuscles. To this succeeds, further inwards, and immediately surrounding the eschar, a zone of *absolute stasis*, in which the blood-vessels are mortified and their blood coagulated, and as a result of course all extravasation is here at an end. The last, the central point of the entire series, is obviously the eschar.*

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* Cohnheim, 'Neue Untersuchungen über die Entzündung,' Berlin, 1873.

I may remind you further of what I formerly stated as to the consequences *of temporarily shutting off the blood from the vessels*. True it is here from the nature of the case impossible to follow with the eye the gradual development of its effects, but in this way we can all the more successfully act on the vessel walls themselves, and subsequently study the influence of the affection on the circulation in them. On removing a ligature which has been allowed to remain tightly bound round a frog's tongue for from twelve to twenty-four hours, all the blood-vessels, as was formerly shown, undergo an enormous dilatation, and the blood flows through them with great velocity. After a time, however, they again contract, whereupon there is a gradual and complete restoration of the normal conditions, without a trace of anything to indicate the disturbance. When, on the other hand, the ligature has been applied for from thirty-six to forty-eight hours, there follows at once, just as in the former case, a primary dilatation with acceleration of the stream; but while the dilatation remains approximately within the same limits, the acceleration after a time makes way for an evident *retardation* of the stream, and this is here too the signal for the peripheral arrangement of the colourless cells in the veins, and for the overloading of the capillaries with blood-corpuscles, on which *extravasation* from the veins and capillaries and œdematous swelling of the tongue very shortly follow. If the ligature is not removed till after about sixty hours, the same oft-mentioned series of phenomena are developed, but the retardation of the stream gradually becomes so considerable that an actual stagnation of red blood-corpuscles occurs in many of the capillaries, and from these proceeds during a period of some hours so enormous a diapedesis of red blood-cells that the swollen tongue appears speckled with red even to the naked eye. It must be noted that, under these circumstances also, the arteries are not in any way involved in the extravasation, however extreme the amount proceeding from the veins and capillaries. That the circulation should completely fail to be restored when the anæmia has lasted still longer, say over three days, will appear only natural, yet you will be interested to learn that the blood then barely forces its way into the commencement of the arteries a little distance in advance of the point of ligature, and that all further motion shortly ceases, so that no more blood reaches the small arteries, to say nothing of the capillaries and veins.*

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* Cohnheim, 'Neue Untersuchungen über die Entzündung,' Berlin, 1872.

Whatever has been shown by these experiments to apply to the frog, is no less applicable to warm-blooded animals, *e. g.* the mammalia. Exposure of the mesentery may also be very readily effected in small rabbits, and with precisely the same results, except that here the death of the vessels and accompanying coagulation, occurs earlier than in the frog, because the external conditions are much less favorable to the experiment, and above all because the vessels of the intestines and peritoneum are far less capable of resistance in the rabbit than in the frog. Thoma† has, however, recently taught us how to overcome these difficulties by employing a suitably constructed hot stage, and has succeeded, after a lengthened examination, in determining the identity of these processes as observed in the dog with those occurring in the frog. The attempt to follow microscopically in the living mammal the effects attending the application of corrosives or the cutting off of the blood-supply, has, despite every effort, so far miscarried; but as though by way of compensation, macroscopic observation is all the more easily carried out. On painting the ear of a rabbit with croton-oil, you fail to detect the least trace of alteration during the first hour. Not until seventy or eighty minutes have elapsed do new vessels begin to shoot up and those already visible to dilate. Then the ear becomes more uniformly red, owing to the contours of the vessels having lost their precision, while *pari passu* a swelling of the concha sets in. A few hours later the ear is vividly and diffusely reddened, hot, greatly swollen, and marked in many places with points and streaks of red. That these are nothing but circumscribed accumulations of red blood-corpuscles or small *hæmorrhages* will be recognised by everyone even without a microscopical examination, but the microscope must be resorted to in order to establish the presence of immense multitudes of lymph-corpuscles, which fill out the interstices of the thickened ear.*

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* Cohnheim, 'Untersuchungen über embol. Processe,' Berlin, 1872.

† Thoma, 'Virch. A.,' lxxiv, p. 360.

The examination of a portion of the rabbit's ear to which a caustic has been applied, when properly carried out, leads to results perfectly according with those observed in the tongue of the frog; and that the effects attending the cutting-off of the blood-supply in mammals are similar to those in the frog will at once be clear to you, on calling to mind the picture I drew on a former occasion of a rabbit's ear so treated. In fact the only difference consists in this, that the respective actions of the anæmia on the vessel walls are much more rapidly established in the rabbit than in the cold-blooded animal. An ischæmia, which in the latter calls forth a mere transitory hyperæmia, causes swelling of the ear of the rabbit; and if the ligature has been applied to the root of the ear for as long a time as would in the frog's tongue be required for the production of extravasation and œdema, hæmorrhage invariably occurs, and indeed it is nothing unusual for the ear to be partially killed.

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* Cohnheim, 'Neue Untersuchungen über die Entzündung,' Berlin, 1873.

Lastly, this, as you notice, unvarying series of changes may also be brought about in the rabbit's ear by the local *action* of unduly high or low *temperatures.* On plunging a rabbit's ear, ligatured at its root, into water at a temperature of from 42° to 44° C., or on allowing it to remain a short time in a freezing mixture till it acquires a temperature of from −3° to −4° C., you observe, immediately after the normal warmth has been restored and the ligature removed, a very intense *active congestion*, which passes off after a time. On the other hand, 48° or 49° of heat, or −7° or −8° of cold, is followed by a more or less intense *rosy swelling, i. e.* by œdema with slight extravasation. The extravasation, however, becomes very copious, and the swelling much more considerable, when the temperature of the concha has been raised to 50°, 52° or been reduced to −10°, −12°. After still greater extremes, hæmorrhages are invariably met with; while, lastly, temperatures of from 56° to 60°, or from −18° to −20°, render the restoration of the circulation impossible. In an ear which has assumed this degree of heat or cold for a few minutes, you will at most only succeed, even after the most careful possible treatment by means of gentle friction, &c., in causing some blood to penetrate a few millimetres into the arteries; further than this it never flows, and the ear is therefore hopelessly doomed to necrosis.*

You see, the phenomena called forth in vascular parts by the most heterogeneous agencies constitute a perfectly regular, constantly recurring series; and they will repay the trouble of a minute analysis, and of referring them to the conditions on which they depend. All the agencies were certainly of such a kind, that the capacity of more or less powerfully affecting the vessel walls must be unhesitatingly ascribed to them; and indeed it was this very consideration which led us to institute the experiments in question. But you may fairly ask—is it then at all possible to explain the whole of the events described on the assumption of such an alteration of the vessel walls, *a molecular change* as we formerly called it? Let us at least make the attempt.

To commence with the *dilatation*—this presents no difficulty whatever to the understanding, on calling to mind the active hyperæmia following direct violence to the walls of the arteries. You know of course that all possible injurious influences affecting the arteries are responded to by a relaxation of the circular muscular coat; and you will therefore regard it as very natural both that slight degrees of the different agencies, *e. g.* ischæmia of short duration and moderate rise of temperature, should bring congestion alone in their train, and also that, as the result of more potent noxæ, dilatation of the arteries and consecutive active congestion are the first changes to set in. In cases of the latter class, however, the action is not limited to atony and congestion. Instead of a gradual restoration of the injured arterial wall, and a re-establishment of the normal circulation with return of the vessel to its normal calibre, the dilatation of the vessels here even increases for a time; *nevertheless the blood-stream is considerably retarded as compared with the normal standard.* This would be inconceivable in a hyperæmia due to local decrease of resistance, so long at least as the arterial blood-pressure continued unchanged; but it becomes, in my opinion, perfectly intelligible if the hurtful agency has produced *an actual internal change in the vessel wall.* We see, in the first place, why the dilatation does not abate, and in the second, why the velocity of the stream diminishes. For since the motive forces and the blood itself have undergone no kind of alteration, the localised retardation of the flow must depend on local resistances. The lumen of the vessels, however, nowhere presents such; on the contrary, the arteries, capillaries, and veins are all of them in every part wide, and even abnormally dilated. Thus there remains, so far as I see, no other course open but to seek the cause of the increased resistance in *a change in the relations between the blood and the vessel walls as regards friction and adhesiveness.* I remind you especially of the fact, on which I have repeatedly and emphatically dwelt, that when arteries have been deprived of blood for three or four days, or exposed to a temperature of 56° C., the blood scarcely penetrates along them, although the lumen is empty, and there is absolutely no thrombus or other contents which might present an obstacle to the inflow of fluid blood. The case of the blood and blood-vessels differs altogether from that of an india-rubber tube with a liquid of any kind flowing through it. It is possible that the inner surfaces of the walls of the dying vessels so adhere to one another that the blood is unable to enter; but however this may be, if the vessel wall can undergo such alteration in constitution as to render the vessel impervious to blood, it appears still easier to conceive that it may, under certain circumstances, delay the forward motion of the blood and retard the stream.

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* Cohnheim, 'Neue Untersuchungen über die Entzündung,' Berlin, 1873.

We have already dwelt on the fact that with the retardation of the blood-stream there must be developed the gradual pavementing with colourless blood-corpuscles, and it is just as easy to understand that an accumulation of blood-corpuscles will occur in the capillaries. It may indeed be said unreservedly that with the increasing alteration of the capillary wall, *i. e.* with the augmentation of resistance, the quantity of blood-corpuscles in the capillaries must accumulate steadily, and the result must be actual *stagnation*. The capillaries are then densely packed with blood-corpuscles; the red, whose number so greatly exceeds the white in the circulating blood, being greatly in the majority. We have here a condition closely approaching *stasis*, *i. e.* the complete standstill of the blood with coagulation, and which may pass into it, yet must nevertheless be kept absolutely distinct. For in stagnation the contents of the capillaries are as yet invariably fluid blood, although its forward motion, its *flow*, is very much weakened; in stasis, on the other hand, the blood is, as has been said, *coagulated*. Stasis, therefore, having once set in, is final and not to be done away with; while stagnation may at any time, the moment its causes cease to operate, give way and pass off.

This must be borne in mind in order to understand subsequent occurrences. On the pavementing of the veins and the accumulation in the capillaries, there rapidly follows, as we saw, the *extravasation of corpuscular elements from capillaries and veins and the increased transudation*. Is it possible to explain these events also by a molecular change in the vessel wall? I venture to think, I believe indeed, if I am not utterly deceived, that this hypothesis offers the simplest possible explanation, and is unattended by any great difficulty. For as regards the transudation, an alteration of the vessel walls is equivalent to *a change in the filter*, and that this cannot be indifferent for the filtrate needs no proof. A quantitative and qualitative change may, or rather must, be undergone by the transudation when the porousness of the vessel walls is altered. That the amount of transudation is actually considerably augmented is most strikingly taught by the tumefaction of the ear or tongue. How far the chemical composition of the transuded liquid is changed we shall have to discuss presently; yet for you the demonstration of such an alteration is superfluous, since the innumerable multitudes of colourless and red blood-corpuscles mingled with the transudation abundantly testify to a complete change of constitution. Only to one point shall I, with your permission, expressly refer, namely, how well the view of the dependence of the alteration in the transudation on a change in the filter harmonises with the facts that however intense the corrosive action, however long the exclusion of blood or the exposure —in short, however powerful the deleterious influences, *not a single colourless or red corpuscle ever extravasates from the arteries*, which, as you know, do not normally maintain any interchange of fluid material with their vicinity.

So far as I can see, we have now shown it to be *possible* to refer all the events, so frequently described, to a molecular change in the vessel walls. Whether they *must* be referred to this cause is another question. Perhaps the vessels play a subordinate part; possibly other factors co-operate with them. That this objection may be raised, I am far from disputing; for the vessels are never alone affected by the agencies we make use of; many other neighbouring structures are also implicated. Nevertheless I believe I can prove strictly *that it is only and solely the vessel wall which is responsible for the entire series of events.* For if we ask ourselves what are the structures liable to be acted on by the agencies employed, we shall have to take into consideration 1, the circulating blood; 2, the vaso-motor nerves; 3, the surrounding tissue; 4, the vessel walls. That in our experiments we are not dealing with an action on the *blood* is evident *a priori*; for it is continually in motion and can never be more than momentarily exposed to the local action; so that such events, developing but slowly as they do, cannot possibly be referred to the blood. Moreover, this assumption is positively excluded by a modification of an experiment, already described when dealing with congestions. If you tightly apply a ligature to the root of a rabbit's ear, from the vessels of which all the blood has been previously removed by the injection of a solution of common salt, and allow the ligature to remain in position for from twenty-four to forty-eight hours; or if you plunge the anæmic ear into hot water or a freezing mixture; the entire well-known series of phenomena, from congestion to tumefaction and extravasation, subsequently sets in, as soon as the blood is allowed to re-enter the vessels of the ear. This occurs just as it did in the other ear, although this time the vessels contained no blood on which the extreme temperature, &c., might have acted. The *vaso-motor nerves* may with equal certainty be excluded. The fact that the vessels are wont, under the influence of the agents employed by us, to dilate very much more than is ever the case in paralysis of the vaso-constrictors or stimulation of the vaso-dilators appears to me to make against their participation. Thus the dilatation and injection of the rabbit's ear, following division of the corresponding sympathetic, increase considerably on painting it with croton-oil, or on introducing it into hot water. Moreover, all the effects that have been described set in in precisely the same way, and with equal promptitude, in parts deprived of all connection with the central nervous system. Not only may the cervical sympathetic be divided in the rabbit, but the entire ear, with the exception of the a. and v. mediana, may be isolated from the remainder of the body by firmly ligaturing it at its root, and for all that reddening and swelling take place precisely as they do after corrosion or scalding. But the chief objection to the theory of a nervous influence is the evident *tardiness* with which the occurrences under discussion are developed under the action of some of the agents employed by us. If, after the application of a corrosive, or after painting with croton-oil, hours must first pass before the vascular dilatation even commences to set in, any one having only a limited acquaintance with nervous physiology will hardly suppose that reflex mechanisms are here concerned; and still less can the effects of ischæmia, which increase so typically with the lapse of time, be referred to nervous influences. Lastly, we have not, in our cases, to do with an action or reaction of the *tissues surrounding* the vessels. For no alterations are observed in the latter except at most such as are of a deleterious character, as for example, coagulation or rupture of the muscle fibres, stoppage of the whipping motion in the ciliated epithelium of the tongue, and the like; and should you be little inclined to attach importance to such morphological proof, I should like to ask, how do you picture to yourselves the force by means of which the tissue, however changed, could bring about these events in the vessels? So far as I know, only anomalies in the processes of diffusion could possibly be attributed to this cause; since, however, these concern gases or liquids alone, the transudation of the solid constituents of the blood would remain altogether unexplained by it. We are therefore compelled *per exclusionem* to return to the *vessel walls*; and if you consider besides in what a definite and regular succession the effects of the agencies increase in severity, from the congestive hyperæmia on till death, you will not, I hope, hesitate to adopt the view I have propounded as your own. According to this view we have here to deal with *a molecular change of the vessel walls*, whose highest degree involves the death of the latter, but whose slighter degrees, on the other hand, call forth a certain typical series of abnormal events in connection with the motion of the blood and the transudation. The sum total of these events, together with their consequences, have been for ages comprised under the notion and name of *inflammation*.

On calling to mind the signs which make their appearance in a part of the body, in which the circulation and transudation has undergone the disturbances so often described, we find they are as follows. Such a part will be (1) *reddened*, owing to the overloading of all its vessels; this condition being complicated in severe forms with small, but numerous, hæmorrhages. It will be (2) *swollen*, because of the increased vascular fulness, but especially because of the great increase of transudation. (3) It will be *painful*, owing to the pressure on, and dragging of, the nerves of sensation by the overfilled vessels and abundant transudation. (4) It will, if situated superficially, be *warmer* to the touch, because a more than normal amount of heat is supplied to it from within by the increased supply of blood. Lastly, (5) its function will be *deranged*, both by reason of the pressure to which the terminations of the motor and secretory nerves are subject from the transudation, and the so essentially altered blood-circulation, in particular the retardation of the capillary stream. Now these five symptoms are nothing more or less than *the cardinal symptoms of acute inflammation*, of which the first four—the fifth, the *functio læsa*, is in reality less a symptom than a resulting condition—had been already established by Celsus; and, despite the advance made in our knowledge of the processes, still serve best to characterise the condition of an inflamed part. We say that a finger or a foot, an ear or a knee, is acutely inflamed when it is *red*, *swollen*, *hot*, and *painful*. This notion of inflammation has been for ages held by the laity; and pathology cannot, as I have just said, better describe acute inflammation than by these symptoms. Nevertheless it will be advantageous to discuss them somewhat more carefully. Only after a detailed analysis of the conditions of their origin can we estimate their whole import, understand their modifications, and learn to comprehend how it is that they may possibly be absent in inflammation.

First, the *redness*, *rubor*—I need hardly repeat that this depends on the abnormal fulness of the vessels of an inflamed part. We have in the larger vessels, the veins and arteries, to deal, as we have seen, with a dilatation of their lumen which is often very considerable; in the capillaries, on the other hand, we have to do, not so much with a dilatation, as with a great accumulation of the coloured constituents of the blood, the red blood-corpuscles. The intensity of the redness is evidently, *cæteris paribus*, directly proportional to the degree of dilatation and overloading with blood. In particular it is absolutely immaterial in this respect whether the blood-stream through the hyperæmic vascular area is accelerated or is retarded; inasmuch as the colouration is at all times solely determined by the amount of blood momentarily present in the vessels. If the inflammatory hyperæmia affects a part whose individual vessels are visible to the naked eye, we speak of an *injection*; as in the mesentery, serous covering of the intestines, conjunctiva: where this is not the case, as *e. g.* in the skin, the redness is termed *diffuse*. The character of the reddening always inclines to be somewhat *dark*, to have a cyanotic tinge; because, for one thing, the dilated veins predominate, but chiefly because, owing to the slowness of the capillary stream, the blood is more completely deprived of oxygen than is normally the case. Yet two factors influencing the degree of rubor come up for consideration, one increasing the other decreasing it. *Hæmorrhage* is the first. The more numerous the hæmorrhages, and the larger the number of extravasated red blood-corpuscles, the more deeply red will the inflamed part appear. The *transudation* must act in exactly the contrary direction; it diminishes the intensity of the redness, because by its increase the rubor is masked and rendered indistinct. Hence the redness will, as a rule, be more conspicuous at the commencement than in the later stages of inflammation, when the voluminous transudation and the multitude of colourless cells will have imparted a grey or at least greyish red tint to the organ. This distinction is the more comprehensible as the red corpuscles preponderate in the neighbourhood of the vessels, where they are permanently located; while the colourless cells, on the other hand, spread themselves throughout the meshes of the entire tissue or reach its free surface. Accordingly in an abscess the deepest reddening is not found in the middle, but precisely where the pus has not accumulated, *i. e.* at the periphery—an actual red zone surrounds the abscess. The redness, it is obvious, can occur only in the vicinity of the vessels supplying the part; in keratitis, therefore, the rubor is not to be sought in the cornea itself, *but in its neighbourhood, i. e.* in the wreath of conjunctival vessels; and in arthritis, not in the articular cartilage, but in the synovial membrane. I shall only say in conclusion that redness of an external part, even when intense, may after death completely disappear, so that a scarlatinal rash, or even an erysipelas or conjunctivitis, often leaves either no trace *post mortem* of its presence, or merely the hæmorrhages which may have chanced to occur.

Second, the *swelling, tumor*—one of its two components, the abnormal fulness of the vessels, requires no further elucidation; the other factor, the *transudation*, must now be discussed. In our experiments on the mesentery and tongue, we were, for reasons easily understood, unable to do more than follow directly the extravasation of the corpuscular elements; the liquid transudation necessarily eluded observation. Yet we inferred the occurrence of an increased transudation from the tumefaction of the tongue which developed *pari passu* with the emigration of blood-corpuscles. But is such a conclusion justifiable? Is it not conceivable that the liquid may transude in normal quantity from the vessels, and that the tongue or ear swells only because—owing perhaps to a disturbance of the lymph-stream—the transudation is not carried off so rapidly and completely as under normal circumstances? A simple experiment will decide; we need only examine the flow of lymph from an inflamed part. After rubbing in croton-oil into the hind paw of a dog, or injecting a half or a whole cubic centimetre of an emulsion of turpentine under the skin of the paw (its proper distribution throughout the tissues of the part being secured by friction and pressure), the paw swells enormously by the following day, it becomes hot, the skin between the toes is intensely reddened and spotted with hæmorrhages, and the dog guards against putting the limb to the ground. On now exposing the lymphatics on the outer side of the leg, you will be surprised by their width and distension, and, a cannula being inserted into the peripheral end of one of the lymphatics, drop after drop of lymph flows away without any rubbing or pressure whatever. There can be no doubt that the lymph-stream is very considerably increased, that it has acquired a volume many times greater than normal. But even this experiment is open to objection, since it is not inconceivable that the circumstances regulating the flow of lymph have been essentially altered since the oil was applied, and more especially since the full development of the swelling. But there is not the least difficulty in demonstrating that the flow is augmented on from the very commencement of the inflammation. To accomplish our purpose it is only necessary to select some exciter of inflammation, which suddenly and from the first affects the vessels, instead of influencing them gradually. Scalding is the simplest method, and the experiment when thus carried out is usually very striking in its results. You introduce a cannula into one of the lymphatics of the leg of a strong and well-nourished dog, and convince yourselves that, as usual, only minimal quantities of lymph can be obtained from the healthy foot. You now encircle the ankle-joint beneath the cannula with an Esmarch's india-rubber tube, and plunge the foot for several minutes into water at about 54° C. till the hairs begin to loosen so as to be removable by a gentle pull. Now take the foot out of the water, dry it, remove the tubing, and immediately the lymph begins to drop most beautifully from the cannula. Only very gradually, during the continuous and equable flow of the lymph, does the inflammatory tumour develop in the course of about an hour. Thus it may be regarded as established that in inflammation, as in venous hyperæmia, a considerable increase takes place in the transudation from the blood-vessels, leading first to an increase in the lymph-stream, and only when the lymphatics are no longer adequate to carry off the transudation, to a swelling of the affected part.*

True, they cannot be the *same* causes that produce in inflammation the increased transudation. In venous hyperæmia it was, as you remember, the disproportion between afflux and efflux, or, in other words, the rise of pressure in the capillaries due to the venous resistance, which caused more liquid to pass through the capillary walls. Beyond question such a disproportion or such an increase of pressure does not exist in the vessels of an inflamed organ. The veins are as wide and pervious as normal, and so little is the blood-stream through them impeded that, as you will soon learn, the rule is for a larger amount of blood to be conveyed through the veins of an inflamed part than under normal circumstances. Nor does the microscope show in the veins of the exposed mesentery or inflamed tongue any trace of that crowding and stagnation of the blood-corpuscles which is so characteristic of venous hyperæmia. But when, in spite of the absence of all abnormal resistance on the venous side, the blood-stream is retarded in the arteries and capillaries, more especially the latter, this can obviously be conditioned only *by resistances which have been interpolated either locally in, or behind, the peripheral arteries,* and which have consumed part of the motive force by which the blood arrives in these vessels. Since, however, not only the velocity, but of necessity the pressure of the blood must be diminished in front of a resistance, it directly follows, *not merely that the blood-pressure is not raised, but that it is even lowered below the normal standard in the arteries, and especially the capillaries, of an inflamed part.*

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* O. Lassar, 'Virch. A.,' lxix, p. 516.

Since we can thus exclude a rise of capillary pressure as the possible cause of the increased transudation, the only remaining factor, so far as I see, is that to which the abnormal resistance in the arteries and capillaries must be attributed, namely, the altered constitution of the vessel wall. The *permeability* of the vessel wall is increased during, and owing to, the inflammation, and it is for this reason that more liquid transudes through it, *notwithstanding the fall in capillary pressure.* But a change in the filter—we were already able to state—leads us to expect, not only a *quantitative,*, but also a *qualitative,* change in the filtrate, so that an examination of the inflammatory transudation from this point of view affords a sort of test of the correctness of the entire theory. To this end the fluid accumulated in the serous cavities in inflammations of the various membranes, or still better, the lymph flowing directly from an inflamed organ, may be employed. Chemical analyses of the various exudations have long been extant in considerable numbers in our literature.* Lymph from the inflamed paw of the dog was examined by Lassar in my laboratory in Breslau.† The results have shown in all fluids a surprising degree of similarity. All these inflammatory transudations are very *concentrated;* a solid residue of 6 and 7 per cent. has repeatedly been found in the inflammatory exudations of man, and Lassar was able to show that on an average 6½—8 per cent. or even more solid constituents is present in the lymph from the inflamed paw of a dog. The salts do not contribute to this stronger concentration, for, as all investigators without exception state, they are contained in pretty much the same relative quantities in the inflammatory transudation and in normal lymph. Consequently the greater concentration is altogether owing to the *albumen,* and thus there is in this respect a direct contrast between the transudations of mechanical hyperæmia and of inflammation; the former is *deficient in albumen,* the latter *rich in albumen,* while the normal lymph occupies an intermediate position. There is still another very striking point of difference between the lymph of mechanical hyperæmia and of inflammation, a difference in their capacity and tendency to *coagulate.* While the former is late in coagulating and the flakes of fibrin are few and delicate; the inflammatory lymph may be with difficulty obtainable, owing to the fact that very often clotting occurs within the short cannula: in the glass receptacle the inflammatory lymph regularly stiffens in a short time to a firm jelly. The factor on which this marked coagulability depends has probably already occurred to you; it is without doubt the richness of the inflammatory transudation *in colourless blood-corpuscles.*

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* Lehmann, 'Physiolog. Chemie,' ii, p. 274; Wachsmuth, 'Virch. A.,' vii, p. 330; Hoppe-Seyler, ibid., ix, p. 245; 'Deutsch. Klinik,' 1853, No. 37; 'Med.-chem. Untersuchungen,' p. 486; C. Schmidt, 'Charakteristik d. epidem. Cholera,' p. 133; Reuss, 'D. A. f. klin. Med.,' xxiv, p. 583; F. A. Hofmann, 'Virch. A.,' lxxviii, p. 250 (contains further references to the literature).

† O. Lassar, 'Virch. A.,' lxix, p. 516.

It was naturally impossible that the presence of corpuscular elements in inflammatory transudations should escape the observation of pathologists since the time when the microscope began to be applied to their examination; and it is also quite comprehensible that the observers' interest should have been centered chiefly on the colourless corpuscles, if for no other reason because they as a rule preponderate so extraordinarily over the red, but more especially because it was believed that the latter could be referred quite simply to small capillary ruptures. During the last few years several theories have been suggested with the view of explaining the manner in which the colourless cells, which received the name of *exudation-* or *pus-corpuscles,* enter the inflammatory effusion; but with a minute exposition of these you will be glad to dispense, now that we have succeeded in directly observing the passage of the colourless corpuscles from the interior of the vessels into the tissue of the vicinity. We now know, not merely that the pus-corpuscles perfectly agree in form and characters with the colourless blood-corpuscles—a point to which Virchow had long ago more than once emphatically directed attention—but *that they are nothing more or less than extravasated white corpuscles.* The only question which can be raised at present is whether *all* the pus-corpuscles in an inflammatory swelling are in reality emigrated blood-cells. I shall have subsequently to discuss more thoroughly this much contested point, so that I may here confine myself to declaring that, so far as I can judge, *no other* mode of origin for the pus-corpuscles has so far been demonstrated with certainty, or that at most the multiplication of pus-cells by division has been rendered probable. If, however, anyone should raise the question, as making against this idea—how then is it possible that the enormous quantities of pus-corpuscles which, in an acute phlegmon, a peritonitis, or a granulating wound,* are often produced in a single day, or an even shorter space, could all of them be derived from the circulating blood—much might be offered in reply. In the first place, please do not underestimate the number of the colourless corpuscles circulating in the blood. Whoever has often observed through the microscope the circulation of a living animal certainly cannot have failed to receive the impression that, in the capillaries and small veins, the quantity of colourless corpuscles is really considerable, and that the proportion of 1 colourless to about 300 red corpuscles, as commonly stated, is absolutely inapplicable to the small vessels. Since, moreover, it has been shown by Alex. Schmidt† that, at the moment of letting blood from a vein, a number of colourless blood-corpuscles fall to pieces and disappear, the determination of the relative or absolute number of white blood-corpuscles in a drop of blood is of no value whatever. But altogether apart from this, it seems to me that the enormous production of pus-corpuscles will be decidedly easier of comprehension if we be permitted to regard the whole organism as concerned in it, and not merely that portion in which the inflammation has been established. No one surely will suppose that all the pus-corpuscles produced in the course of a phlegmonous inflammation were already present in the blood at the commencement of the process. On the contrary, it is beyond doubt that, even under perfectly normal conditions, new colourless corpuscles are being constantly supplied to the blood to replace those that have been used up; and in inflammation it would only be a question of an abnormally increased formation, and supply, of colourless cells. And, in fact, many statements of recent date completely harmonise with this result. According to these the number of colourless corpuscles in the blood is considerably increased in inflammation.[*] Moreover, the numerous older observations of physicians, who found a large amount of fibrin in the blood in inflammatory diseases, a so-called *hyperinosis*,[†] when interpreted in the light of our present views, signify nothing more or less than a considerable increase of colourless blood-corpuscles. As to where and how this multiplication of white blood-cells in inflammation takes place, we are unable—owing to the obscurity still prevailing as to the entire life-history of the colourless blood-corpuscles—to adduce adequate and certain data. Yet there is much in favour of the view that the same organs, on which very probably the formation of lymph-corpuscles is physiologically incumbent, receive greater calls on their activity in inflammation. At least, nothing is more usual than for the *lymphatic glands* in the neighbourhood of an inflamed part to be more or less swollen; and even the *spleen* is found, in many of the more extensive inflammations, in a condition of pronounced hyperplasia.

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* Billroth, 'Oesterr. med. Jahrb.,' Bd. xviii, Heft 4 and 5.

† A. Schmidt, 'Pflüg. A.,' ix, p. 353.

In addition to the pus-corpuscles there is constantly present in the inflammatory transudations—or as they are briefly called, *exudations*—a quantity more or less large of *red* blood-corpuscles. That these also reach the exudation, without any solution of continuity or rupture of vessels, by passing through the uninjured walls of the capillaries and smallest veins by *true diapedesis*, has been determined by direct microscopic observation. The time occupied in the passage of a single red blood-corpuscle through the capillary wall varies extremely. Sometimes the transit is excessively slow, at other times three or four, or more, corpuscles in succession glide in a few minutes through a part where, immediately afterwards, the blood-stream, with its corpuscles, flows heedlessly by. Some of the extravasated red blood-corpuscles remain isolated on the external surface of the capillaries, while others become aggregated into little heaps, which are then recognisable by the naked eye as punctiform hæmorrhages. Sometimes, however, they may, it is evident, be seized and borne away by the stream of transudation, and hence it is not to be wondered at if they are present in the fluid of a pleuritic or pericardial effusion. That the red blood-corpuscles constitute, as a rule, by far the smallest part of the corpuscular elements in exudations, and are very greatly outnumbered by the pus-corpuscles, is simply explained by the fact that the red corpuscles extravasate from the capillaries alone, while an abundant source of white corpuscles is presented by the veins as well as the capillaries. Still the red blood-corpuscles in the exudation will always be more numerous the denser the network of capillaries in the affected organ, *e. g.* in an inflammation of the lung as compared with one of the subcutaneous fat. When dealing with the "redness," I mentioned that in the earlier stages of inflammation their number is, at least relatively, greater in comparison with the colourless cells; in the later stages the pus-corpuscles never fail to preponderate immensely, as is evident both to the naked eye and on microscopic examination. But by further calling to mind that from the capillaries with almost stagnant contents red blood-corpuscles almost exclusively extravasate, you will be able to directly estimate the circumstances in which their numbers in the exudations will be specially increased. This will be the case where the capillary walls are powerfully affected by the agent exciting inflammation, and in consequence the circulation in these vessels is exceptionally interfered with; in other words, *in very severe inflammations.* Here the exudation may even assume a true *hæmorrhagic* character.

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[*] Virchow, 'Gesammelte Abhdlg.,' p. 180; Malassez, 'Arch. d. Physiol.,' 1874, p. 32; Nicati u. Tarchanoff, 'Arch. d. Phys.,' 1875, p. 514.

[†] Andral u. Gavarret, 'Untersuchungen über d. Mengenverhältnisse d. Faserstoffs, &c., im Blute bei verchied. Krankheiten,' übers. von Walther, 1842; J. Vogel in Virchow's 'Handb. d. spec. Pathologie,' i, p. 396.

No other corpuscular elements are found in fresh inflammatory transudations, excepting of course accidental admixtures, of which a variety may be met with according to the locality. Let it be clearly understood—*in fresh.* For we shall soon come to deal with the fate of the pus-corpuscles in the exudations, when some time has elapsed since their origin, and shall then have to make mention of Gluge's corpuscles, epithelioid and giant-cells, &c., amongst the products of inflammation. Not one of these elements is present in fresh exudations, their formed constituents being limited, as has been said, to blood- and pus-corpuscles. But even these may, in an exudation of undoubted inflammatory origin, be so small in quantity that the fluid is almost as clear as water. Thus the lymph which drops from the cannula immediately after the scalding of a dog's paw is unusually poor in cellular elements; only after a time does their number increase, and may then certainly be very considerable. I have already stated that the rabbit's ear swells, becomes œdematous, on exposing it to a temperature of 48° or $-7°$ C., but that an insignificant number of colourless or of red blood-corpuscles passes into the tissues. These two examples clearly indicate under what circumstances inflammatory transudations will be *poor in cells*, namely, first in the *early stages* of an inflammation, which yields later on a very plentiful cellular exudation; and second, in inflammations of *slight intensity*, in which the alteration of the vessel-wall is only just sufficient to permit an increased transudation of fluid, but does not allow of a plentiful extravasation of corpuscular elements. For that in these cases also the causes of the augmented transudation are identical in kind, is shown most clearly by the perfect agreement in chemical constitution of the transuded fluid and the exudation rich in cells. The transudation is always *concentrated* and *highly albuminous*, although, it is true, the dried residue will be increased with the increase of pus-corpuscles.

But to go a step further. There is in principle nothing against the assumption that inflammations also exist, in which the transudation altogether fails to be increased, or at least does not appear in the shape of a *tumor* or tumefaction. Whether it is at all possible for the whole effect of an inflammatory agent to be restricted solely to a dilatation of the vessels and a retardation of the blood-stream, appears to me very doubtful. If the constitution of a vessel-wall be altered to such an extent that it opposes to the blood-stream a certain amount of abnormal resistance by increased friction, &c., its permeability may well have increased also; at any rate

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experience, as far as is at present known, gives us no title to separate the two in inflammation. But it can hardly be disputed that the increase of transudation in inflammation need not necessarily on every occasion exceed the measure which the lymphatics are capable of carrying off. The lymph-stream will then be augmented while the inflammation lasts; but tumefaction or *tumor* of the inflamed organ does not develop. Inflammation of this kind is probably not at all rare in human pathology; it seems probable enough, at least, that a whole series of inflammatory skin affections, in particular the *acute exanthemata*, are to be classed here—inflammations in which the trifling amount of swelling most strikingly contrasts with the intense redness and heat.

While accordingly the *tumor* of inflammation is not absolutely constant, the *mode of its manifestation is extraordinarily variable.* For this depends essentially on the anatomical structure of the inflamed part. So-called parenchymatous organs, as for example the muscles, testicles, liver, parotid and other glands, &c., swell, when inflamed, in their entirety; and the swelling is exactly proportional to the amount of the exudation, except when held in check by some enveloping unyielding membrane or capsule. The exudation is here situated in the meshes of the supporting, so-called interstitial, connective tissue, because this also carries the blood-vessels and most readily allows of distension by fluids. Accordingly, when inflammation occurs in an organ made up exclusively of connective tissue the exudation is lodged in its meshes; it infiltrates them. So it is in phlegmonous inflammation, where the interstices of the subcutaneous adipose tissue are its seat; and in meningitis, where those of the pia mater lodge it. The same thing occurs in the substance of the cornea in keratitis; but in fresh cases of this disease the thickening is as a rule inconsiderable, owing to the slight degree to which the tissue is distensible, while the infiltration shows itself rather as a cloudiness: yet the latter is also to be attributed solely to the presence of pus-corpuscles and transudation in the cornea, inasmuch as the refractive power of these differs from that of the corneal tissues. Into *cartilage*, which contains no distensible meshes or canals, exuded fluids or pus-corpuscles cannot of course effect an entrance;

hence in articular inflammations the exudation is found in the cavity of the joint, but never in the cartilages. If, on the other hand, an organ having a free surface, or one whose vessels border on a cavity, be inflamed, the products of inflammation, when sufficiently accumulated, will be exuded on the free surface; and here we speak of an *exudation* in the strict sense. This is the case in all the serous membranes as well as in the dura mater; in the choroid, the exudation from which mingles with the vitreous humour; in the periosteum and perichondrium. For though the surfaces of the membranes last mentioned are not, it is true, in an anatomical sense free or bordering on a cavity, yet the inflammatory product *exudes* from their tissues, and is lodged between the membrane and the bone or cartilage, because these situations oppose a less obstacle to the accumulation of the exudation than does the very dense tissue of the periosteum itself. For this is the principle which regulates the accumulation—*the product of inflammation accumulates wherever it finds the least amount of resistance.* Thus in pneumonia it must very quickly reach the alveoli and fill them, because it has no room in the alveolar septa; and we ought really to speak of a *pneumonic exudation*, instead of employing the term *infiltration*, with which in this connection we are long familiar. It will also be clear from the above principle why, in places where the passage of the exudation on to a free surface is prevented by a very dense covering, a *vesicle* or *pustule* arises. Lastly, in organs communicating freely with the outer world, and having an unobstructed outlet, the inflammatory product will of necessity flow off or mingle with the secretions; as *e. g.* in all *mucous membranes*, and in the *kidneys*, when during inflammation the urine contains albumen and corpuscles. Add to this the variable composition of the inflammatory transudation, as I have attempted to describe it to you, and you will certainly acknowledge that the *tumor*, though identical in its mode of origin, is, in the manner of its manifestation, one of the most variable signs of inflammation.

We now come to the third point—the *pain, dolor*. Since this, as already pointed out, is dependent on the dragging and pressure to which the sensory nerves of an inflamed part are exposed through the over-filled vessels, but especially through the exudation, the degree and severity of the pain will be determined—(1) by the richness of the part in question in sensory nerves; (2) by the distensibility of the organ, *i. e.* on whether or not the exudation when poured out is itself subjected to a high pressure; and (3) by the amount of the exudation. In organs which are poor in sensory nerves, as the kidneys and many mucous membranes, even violent inflammations may run an almost painless course, while in the serous membranes, which are plentifully supplied with sensory nerves, the inflammatory *dolor* is usually very severe. On the other hand, phlegmonous inflammations are most painful when occurring beneath fasciæ; and you will all have experienced what agony is occasioned by inflammations under the finger-nail. Moreover, the pain frequently travels along the course of the sensory nerves, and is radiated to other branches. The character of the pain may differ greatly; very commonly—especially in strongly distended parts—it is markedly *throbbing*, synchronously with the pulse, because every pulse-wave necessarily increases the pressure on the nerves.

The fourth symptom—the *heat, calor*—demands an accurate examination. The degree of *heat,* which, in warm-blooded animals with a naturally high temperature, is presented by a part to the investigator, is the product solely of the supply and the loss of heat—in such parts at least where caloric is not itself produced. The medium by which heat is supplied to a part is, as you know, the blood. Now the principal heat-producing foci—the heart, liver, and other glands, and the large masses of muscle—are deeply situated, while by far the greater portion of the loss takes place at the surface of the body, viz. from the external parts. From this it follows that the deeply placed internal organs, whose direct loss of heat is very trifling, have under all circumstances the highest temperature—a temperature equal to that of the blood itself; while, those that are situated superficially, in which practically no caloric is produced, will be cooler the more heat they give off, and the smaller the amount conveyed to them by the blood. We formerly saw how, in harmony with this, superficial parts become cooler in anæmia and in venous hyperæmia, and warmer in arterial congestion. For in the first two forms of circulatory disturbance, not only do the arteries supply very little blood, but the loss of heat is facilitated by the retardation of the flow. In active congestion, on the contrary, the supply of arterial blood is increased, while the augmented velocity more than compensates the loss of heat. Now what is the condition of affairs in inflammation? Here there is, on the one hand, an increased supply of arterial blood; for the arteries are dilated, and all the vessels in a condition of marked hyperæmia. There is, on the other hand, a diminution in the velocity of the blood-stream; so that consequently the loss of heat is facilitated, while at the same time the heat-supply is augmented. In all other circulatory derangements both factors act, as you see, in the same direction, while in inflammation they act in opposite directions. What may be inferred therefrom as to the condition of individual organs in inflammation? Above all, that the action of these factors will *never be to increase the temperature of internal organs*, except the general or blood-temperature is at the same time increased by the inflammation; for since the internal organs have the same degree of heat as the blood, an increased supply of this fluid cannot add to it. In the next place, that in superficial parts the temperature may be augmented as the result of inflammation, but *can never exceed the blood-temperature, indeed can never quite equal it.* Whether it is raised at all will depend on which of the two factors just mentioned preponderates; on whether, for example, the supply of heat owing to the hyperæmia is greater than the loss of heat due to the retardation of the blood-stream. This is very possible, but the contrary is conceivable also; and it is even not impossible that both factors may maintain an exact equilibrium. In fact this question cannot in my opinion be decided *a priori*; an appeal must be made to experience—to experiment. We can measure both the temperature of a part, and the quantity of blood flowing through it in the unit of time. Surgeons have long known that, on cutting into an inflamed part, a more copious bleeding generally results than when a normal tissue is incised; but an accurate determination of the quantity of blood in question may be made without any difficulty whatever. By setting up a severe inflammation of one fore paw of a dog, either by scalding, painting with croton-oil, subcutaneous injection of an emulsion of turpentine, or other means, and then introducing on each side a cannula into the peripheral ends of the large veins running along the back of the fore-legs, you can very conveniently compare the quantities of blood flowing, in a given number of seconds, from the healthy and inflamed paws. In order to secure greater accuracy in the results, you will certainly do well to apply on each side a venesection bandage in the neighbourhood of the elbow joint, or still better a tight ligature round the leg, omitting the a. brachialis. The result is highly instructive. While, for example, on the sound side of a large dog, 4½ c.c. of blood flows away in ten seconds, there escapes during the same time, from the vein of the inflamed limb, 8 c.c. *Occasionally the quantity on the inflamed side is more than double that on the other;* and indeed where the inflammation is quite recent, you may occasionally satisfy yourselves that it is almost as large as it would be on the sound side were the plexus axillaris divided. But even in inflammations of the second or third day, there flows, as a rule, a considerably larger quantity from the affected than from the unaffected paw. Yet this result, you will please notice, is by no means constant. That when the inflammation is still older, and commencing to subside, the difference should gradually disappear, is of course nothing remarkable. But you may occasionally find—and particularly in very severe inflammations—that very soon after their commencement the quantity of blood flowing from the affected leg is even *smaller* than on the other side—a result which,—I may at once add—can usually be explained by the rapid setting in of more or less extensive gangrene of the foot. I have also often noticed the absence of any increase in the blood-stream in very severe suppuration of the paw.

On comparing these estimations of the quantity of blood flowing from the inflamed paw in the unit of time with the value shown by a thermometer placed between the toes, you will find, in all cases where an increased amount of blood flows out of a cannula in the vein, the temperature of this side higher than that of the sound one. Nor is the disparity by any means slight. It is not uncommon for the inflamed paw to be 6 to 8 or even 10° warmer than the other. But still more noteworthy, as I think, is the absence of this rise of temperature in those cases in which the quantity of blood passing through the diseased leg is not increased; the affected paw may then be strikingly cool to the touch as compared with the sound one. Taking all in all, you will admit that the results agree with our assumption as perfectly as anyone could expect.

But these thermometric measurements teach us further—that, however much the temperature of the inflamed paw may exceed that of the sound one, *it never acquires the temperature of the blood, nor even that of the rectum;* it always falls short of this by at least one or two degrees, and often considerably more. Almost a century ago the celebrated pathologist, J. Hunter,[*] came to the same conclusion, and summed up his investigations in the proposition—"A localised inflammation cannot raise the warmth of a part above the temperature which is found at the source of the circulation." Yet the correctness of this doctrine has since been disputed by J. Simon[†] and C. O. Weber[‡], who consider they have found, on the contrary, that peripheral inflammatory foci, produced in part by fractures of bone, in part by the subcutaneous injection of croton-oil into an extremity, are warmer than their arterial blood-supply. You will be ready to dispense with an account of the far-reaching inferences, which the above-named authors have drawn from these their observations, on my informing you further that, to say nothing of the experiments just now discussed, the results of Simon and Weber have been corrected by very competent authority. By employing more exact methods—especially the thermo-electric estimation of temperatures—H. Jacobson and his scholars[§] found that a rabbit's ear is, during the course of the most violent croton inflammation, considerably, often several degrees, warmer than the sound ear of the other side, but that it always remains very much cooler than the rectum or vagina of the animal; that, further, an inflammation of the deep muscles of the upper leg in the dog produces at most a very trifling, and often no, rise of temperature as compared with the sound leg; and that, lastly, in fibrinous pleuritis or peritonitis in the rabbit, the temperature of the inflamed cavity is invariably either the same as, or less than, that of a healthy cavity, or of the heart of the animal. Moreover in the subsequent course of the inflammatory process, the corresponding portion of the sound limb often proved to be the warmer. The results so established in inflammations produced experimentally in the dog and rabbit have since then been repeatedly confirmed by means of thermometric measurements carried out in various surgical inflammations in the human subject.*

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[*] J. Hunter, 'Abhandlung über Blut, Entzündung und Schusswunden,' übers. von Braniss., 1850, p. 552.

[†] J. Simon, in Holmes's 'System of Surgery,' art. "Inflammation," i, 42.

[‡] C. O. Weber, in Pitha-Billroth's 'Handb.,' i, Abth. i, p. 381.

[§] H. Jacobson, 'Virch. A.,' li, p. 275; Jacobson u. Bernhard, 'Med. Ctbl.,' 1869, p. 289; Laudien, 'Ueber örtliche Wärmeentwicklung in der Entzündung,' 1869.

The fifth point, the *functio læsa,* however serious for the individual organs affected by it, may in a general discussion of the subject be briefly disposed of. For that a part which is painful, swollen by exudation or infiltration, and which has undergone such essential changes in its circulation, must also be disturbed in its functions, is really self-evident. When you consider, for example, that in an inflamed organ not merely are the sensory nerves but also those centripetal fibres whose excitation calls forth reflex processes, together with the motor and secretor nerves, pressed upon and dragged by the overloaded vessels and the exudation, nothing will appear more natural than that the inflammation should, under certain circumstances, be accompanied by abnormal reflex processes. Thus in inflammations of muscular organs the contractile power is impaired; and when the glands are similarly involved the function of secretion is interfered with, or the quantity and composition of the secretions altered. The nature of these alterations and disturbances will be discussed in connection with the pathology of the individual organs. And similarly we shall have to consider the nutritive disturbances which cells and tissues may sustain in inflammation, when we come to deal with the pathology of the metabolism of the tissues.

If regard be had to the details just communicated, the symptoms or signs which may be expected to be present in an inflamed part as well as the circumstances in which one or other of them may be absent will naturally suggest themselves. In parts poorly supplied with nerves the inflammation runs a painless course, and, similarly, the temperature of internal organs is not increased. Non-vascular parts, when inflamed, cannot be reddened; and where the amount of transudation does not exceed the capacity of the lymphatics, even the inflammatory tumor may fail to appear. How various are the modes of manifestation of the tumor we have already carefully discussed; and your attention has just now been directed to the multiplicity of the functional disturbances attending inflammation of the different organs. A still more thorough account of the positive diagnostic signs of the inflammatory process appears, accordingly, to be impossible as well as superfluous. On the other hand, it may be advantageous to accentuate the differential characters distinguishing inflammation from the other circulatory disturbances which formerly occupied our attention, and which in truth have many points of similarity to it. In this way we shall be able to throw the peculiarities of the inflammatory process into still sharper relief.

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* Schneider, 'Med. Ctbl.,' 1870, p. 529; Huppert, 'Arch. d. Hlk.,' 1875, p. 73.

The likeness to *active hyperæmia* strikes the eye most of all. Here, too, we have a hyperæmia conditioned by a dilatation of the arteries, and produced in many cases by influences acting directly on the vessel wall, as in the congestions due to high temperature, following temporary ischæmia, or mechanical violence. The part affected is reddened and hot, not uncommonly painful, at the same time slightly tumefied, while its function may also be deranged. The rise of temperature may be even more considerable than in inflammation, inasmuch as in fluxion the compensating factor, the increased loss of heat due to retardation of the stream, is absent. All the remaining symptoms, however, are much more vividly manifested in inflammation. Pain and functional disturbance are always more marked in the latter; moreover, the redness of fluxion never acquires that intensity which is seen in inflammatory hyperæmia, so that, as I formerly stated, a part whose vaso-motors are divided becomes considerably more *hyperæmic* on setting up inflammation.

Besides, the redness of congestion is brighter, of inflammation darker, more livid. But more important unquestionably is the fact that, except in the tongue (cf. p. 14), *transudation is never increased by simple congestion, while in inflammation this increase is never absent.* Hence congestive swelling does not exceed the moderate bounds set it by the varying fulness of the blood-vessels, while the inflammatory tumor may assume enormous dimensions. True, it does not always do so, and in certain inflammations of slight intensity this differential character may, as we have seen, be omitted. The increase in the lymph-stream can, however, hardly fail to be found in these inflammations—a circumstance of which, it is true, no advantage can be taken in arriving at a differential diagnosis in man. In addition to the other factors that have been adduced, the chief weight must then be laid on the condition of the organism as a whole, which in inflammation invariably sympathises much more strongly than it does in simple congestion. The later local changes afford a further distinction; of these I shall soon give a fuller account.

In the second place, passive hyperæmia or *venous stagnation* has to be considered. Here, too, there is a reddening due to overloading with blood, a reddening, moreover, which more closely resembles the inflammatory form by reason of its livid hue. There is also an increase of transudation, that is, a tumor. Pain may likewise be present, and functional disturbance will always be found. On the other hand, *calor* is invariably wanting, and, again, the constitution of the tumor is totally different from that in inflammation. In the œdematous fluid of mechanical hyperæmia cellular elements are almost entirely absent, or are present only in the proportions found in every normal transudation, though, where the stagnation is intense, *red* blood-corpuscles are met with in smaller or larger numbers. In the inflammatory exudation the latter are not wanting, but pus-corpuscles are always present in addition, and sometimes in enormous quantities. But the œdema of stagnation cannot be confounded even with the products of an inflammation of the most trifling severity, nor with those of the earliest stage of severer forms, in both of which a liquid containing few corpuscles is secreted from the vessels, for the former is a *very thin* fluid, while the inflammatory transudation, on the contrary, is a *concentrated* one.

After this exposition it will not be necessary to repudiate in detail those theories of inflammation which till a few years ago were universally accepted, and some of which are still held by a few authors, either in their entirety or in modified form. In view of the extreme frequency of inflammatory processes, and of their predominant importance throughout the whole of special pathology, the attention of practical and theoretical pathologists of all ages could not, of course, fail to be attracted by them. Indeed, one is perhaps justified in saying that it is the interpretation of inflammation which has formed the starting-point and goal of all the systems and schools of medicine that have, in the course of centuries, succeeded one another. Of these theories of inflammation only few, of course, have been able to maintain a footing up to our time, and among them the *neuro-humoral* occupies the chief place. This theory seeks, as its chief object, to explain the circulatory disturbances in inflammation, and aims therefore at establishing on a rational basis the occurrence, on the one hand, of the hyperæmia, and, on the other of the retardation of the blood-stream; in regard to the latter of which it has long been known that it may in the capillaries amount to stagnation. The neuro-humoral theory of inflammation presents itself in two modified forms, an *ischæmic* and a *paralytic*. According to the former, which has been explained and elaborated by Cullen, Eeisenmann,[*] J. Heine,[†] and in greater detail by Brücke,[‡] it is to the *contraction* of the afferent arteries of a part, reflexly called forth by the excitation of sensory nerves, that the further circulatory disturbance, in particular the slowing of the capillary stream, is due. According to the second, which no one has done more to perfect than Henle,[§] it is, on the contrary, a reflex *relaxation* and *dilatation* of the arteries that occasions the inflammatory hyperæmia. Now that these two theories are inadequate to render the circulatory disturbance in inflammation comprehensible, requires in our case no special proof. Narrowing of the arteries can only, as you know, produce anæmia, or, when extreme, necrosis; or, again, when the secondary conditions are favorable, hæmorrhagic infarction; and, with respect to the active hyperæmia, I have just been dwelling again on the facts that only exceptionally can it increase transudation, and that it, as a rule, gives rise to nothing bearing the least resemblance to the inflammatory tumor. But we now know, besides, how it was possible for such excellent observers as the above-named to fall into such apparently palpable errors; they failed to discriminate sharply between the circulatory *disturbances setting in immediately on the application of the exciter of inflammation*, and *the disturbances which are strictly inflammatory*. It is perfectly true that when any more or less active so-called *irritant* is applied anywhere, the arteries undergo sometimes contraction, at other times *dilatation*, and, again, at other times, contraction followed by dilatation, and there may be a great deal of interest in investigating the conditions in which one or other of these events ensues, as has recently been done by Saviotti[*] in a paper marked by great industry. *With inflammation, however, these phenomena have nothing to do*, for it can be shown in the most positive manner that they may be present without subsequent inflammation, and—what is still more decisive—that inflammation very often sets in in the absence of these antecedents. After vigorously pinching the tongue of a frog with a forceps, a very strong active hyperæmia of the entire half of the organ is wont immediately to appear; this subsides after a time without the development of any other condition whatever. You may, indeed, produce a much stronger active hyperæmia, and one which develops with extreme rapidity, by touching a small part of the surface of the tongue with the button of a red-hot sound; this hyperæmia also gradually subsides without leaving the slightest trace behind it, not even around the eschar is inflammation set up.[†] Now call to mind our experiments on the rabbit's ear. After painting with croton-oil or burning with nitrate of mercury, more than an hour elapsed before even the slightest beginnings of a hyperæmia could be detected, and there ensued, nevertheless, an inflammation of intense violence. Accordingly, the belief in an intimate connection between these, often very conspicuous, early appearances in the vessels and the subsequent inflammation must be unconditionally surrendered. The phenomena, which are no doubt partly reflex, and partly the result of mechanical injury of the vessels, may, it is true, pass on without a break into actual inflammatory disturbance of the circulation, as could be directly traced in the mesentery of the frog, but this simply means that *a molecular change in the vessel walls* has very rapidly become associated with the simple relaxation of the muscular coat, *the atony*. In very many cases, however, the tonus is relaxed only gradually, the relaxation strictly keeping pace with the development of the alteration of the wall, which latter always is, and continues, the main element.

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[*] Eisenmann, 'Haeser's A.,' 1841, p. 239.

[†] J. Heine, 'Physiol.-path. Studien.,' 1842, p. 156.

[‡] Brücke, 'Archiv. f. phys. Heilk.,' ix, p. 493.

[§] Henle, 'Zeitschr. f. rat. Med.,' ii, p. 34; 'Handb. d. ration. Pathol.,' Bd. ii. p. 417; Stilling, 'Physiol.-pathol. und medicinisch-praktische Unter-über die Spinalirritation,' 1840.

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[*] Saviotti, 'Virch. A.,' l, p. 592.

[†] Cohnheim, 'Neue Untersuchungen über die Entzündung,' Berlin, 1873.

These facts are sufficient, in my opinion, to show that nervous influences, with whose potency elsewhere we are familiar, are not decisive of the process of inflammation. And how, further, can it be reconciled with this hypothesis that parts, unconnected with the remainder of the body except by means of their principal vessels, may undergo inflammation; how it is to be explained that, in the frog, the tongue may become inflamed, even when the brain and medulla oblongata are completely destroyed? An abundance of analogous examples are presented by human pathology also. An eye whose trigeminus is paralysed, or an extremity with complete paralysis of motion and sensation, is not for this reason inflamed, *nor is it by any means protected against inflammation.* By what reflex mechanism can the occurrence of a severe purulent keratitis in a completely anæsthetic cornea, or of an erysipelas, a phlegmon, in a leg deprived of sensation, be explained? At most by the mediation of the ganglia in the wall of the vessels, whose possible participation we shall very soon discuss.

Not only have parts of the body, deprived of every nervous connection with the central organs, no immunity from inflammation, but they become inflamed, as has long been known

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to physicians, *very readily*, much more readily, apparently, than parts whose innervation is perfect. Few facts in experimental pathology are more certain than the occurrence of violent inflammation in the eye of a rabbit within twenty-four to forty-eight hours after division of the corresponding trigeminus, or that rabbits both of whose vagi are divided perish from pneumonia within two or three days. There are, moreover, certain affections of the skin of an undoubtedly inflammatory character, which, like herpes, appear in vesicular form, and which accurately correspond in seat and extent with the distribution of certain nerves. Despite what has been said, do not these facts point to the co-operation of nerves in the process of inflammation? There are, indeed, many authors, who have attributed to certain specific nerves, the so-called *trophic* ones, an essential importance in this direction; according to some it is their quiescence, according to others their stimulation, that calls forth inflammation. But, however weighty may be the names* amongst the champions of this doctrine—I mention, for example, Charcot's—I do not hesitate to declare myself against it. In such of the so-called trophic inflammations as have been carefully investigated, proof positive could be afforded that they owe their origin to conditions quite other than paralysis or excitation of trophic nerves. With respect to *pneumonia after division of the vagi*, it was years ago shown by Traube† in a series of ingenious experiments, that the affection is due simply to foreign bodies, remains of food, buccal mucus and the like, which slip into the lungs through the paralysed and gaping glottis—a result which has since been assailed in vain, and which more recently has even received in many directions still stronger support. Thus Steiner succeeded in preventing the occurrence of pneumonia by simply placing the rabbits continuously on their backs after division of the vagi, and thus making it possible for the fluids of the mouth to escape through the mouth and nose.[*] The same thing applies to the trigeminus-keratitis, or as it is also called by ophthalmologists, the *neuro-paralytic inflammation of the cornea.* Here too the keratitis is attributable solely to the circumstance that the anæsthetic eye cannot protect itself against accidental injury. It is quite unnecessary to do as Snellen did, and stitch the ear over the insensible eye, in order to prevent the occurrence of keratitis; the same object may be perfectly secured by using any other protective covering you please, a common pipe-lid for instance, which is fastened in front of the eye. Nor is this all; for Senftleben has shown that in this form of keratitis we are not dealing with a direct inflammation. The earliest change is invariably an evident *necrosis* of the cornea, called forth by some trauma or other, which the unprotected eye failed to ward off; and only after necrosis has first occurred does the secondary inflammation set in.[†] Accordingly the trigeminus-keratitis cannot in any way be utilised as an argument for the existence of a trophic inflammation; and if, as we have seen, the theory has, in both these apparently so conclusive cases, failed to stand the test of a critical examination, I think we shall do well, in the case of herpes zoster also, to wait for a careful anatomical or experimental examination before basing such far-reaching conclusions on this isolated fact.

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* Samuel, 'Die trophischen Nerven.,' 1860; Tobias, 'Virch. A.,' xxiv, p. 579; Schiff, 'Untersuchungen über die Physiol. d. Nervensystems,' 1855; Charcot, 'Klinische Vorträge über d. Krankheiten d. Nervensystems,' übers. v. Feltzer, 1874, Bd. i, p. 1; Brown-Séquard, 'Experimental Researches applied to Physiology and Pathology,' 1853; O. Weber, 'Med. Ctbl.,' 1864, No. 10; Kaposi, 'Wien. med. Anz.,' 1875, 11 Novbr.

† Traube, 'Gesammelte Abhandl.,' Bd. i, pp. 1, 113.

The *cellular theory of inflammation* propounded by Virchow[‡] has long enjoyed a popularity, if possible, still greater than the neuro-humoral. According to it, the events connected with the vessels are far from being the main element in inflammation. They occupy only a subordinate place, and are to be regarded as secondary; while the genuine central point of the entire process must be sought in the *tissue-cells* of the affected part. These are supposed to swell and enlarge on exposure to the inflammatory irritant, and then to give birth to new cells, the pus-corpuscles. The necessary material is of course abstracted from the increased stream of transudation, which itself is explained by a sort of *attractive influence*, supposed to be exerted by the tissue-cells on the vessels, or their contents. The cells which the irritant had caused to enlarge induce the neighbouring vessels to dilate, and to allow of an increased transudation. You observe that this theory—of which, it is true, the merest outline has been given—introduces into physiology a principle discovered *ad hoc*, and having no analogy elsewhere,—that of *an attraction of the tissues or tissue-cells on the vessels and their contents.* For even if we disregard the circumstance that the mechanism of glandular secretion is applicable to the glands alone, no comparison with that process can be made here; for Heidenhain* has shown that, in spite of the fullest functional capacity of the gland-cells, and the perfect integrity of the circulation, poisoning of the secretor nerves is sufficient to completely suppress the increase of transudation. Moreover, an attractive influence of this kind could at most relate only to fluids, in the case of which we are acquainted with certain analogies in the phenomena of diffusion. But how the tissue-cells are to set about enticing the colourless or red corpuscles out of the vessels, passes, as I told you, at least my comprehension. Add to this that it can be shown with absolute certainty how, in very many cases, not only is marked hyperæmia present, but also very considerable transudation, before the slightest change has occurred in the tissue-cells. The so-called serous inflammations have long been cited in illustration of this fact by the clinicians in opposition to Virchow; and you yourselves need only call to mind the slight inflammations of the ear, following heating to 48° or a temporary ischæmia, to acknowledge the correctness of the statement just made. Here there were really considerable doughy swellings, although no evidence of any change was presented by the cells of the tongue or ear, and extremely few pus-corpuscles were met with in the tissues; while the few that were present were situated in the immediate neighbourhood of the veins and capillaries. This holds good not merely in inflammations of vascular parts, but is equally true of inflammations of so-called non-vascular ones, on which the edifice of the cellular pathology has been built up. The hyperæmia of the conjunctival vessels and circumferential plexus invariably precedes the clouding of the cornea or the appearance of pus-corpuscles in its tissue; and is very extensive, or more circumscribed, in proportion to the intensity of the developing keratitis.

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[*] Genzmer, 'Pflüg. A.,' viii, p. 101; Frey, 'Die pathol. Lungenveränderungen nach Lähmung. d. N. vagi,' Leipzig, 1877; Steiner, 'Arch. f. Anat. u. Physiol.,' Physiol. Abth., 1878, p. 218. Cf. also these lectures, vol. ii, sec. 4, 1.

[†] v. Graefe, 'Arch. f. Ophthalm.,' 1, p. 206; Büttner, 'Zeitschrift. f. rat. Med.' (3), Bd. xv; Meissner, ibid. (3), Bd. xxix; Snellen, 'Arch. f. d. holl. Beit.,' i, p. 206; Senftleben, 'Virch. A.,' lxv, p. 69, lxxii, p. 278.

[‡] Virchow, his 'Archiv,' i, p. 272, iv, p. 261; 'Handb. d. spec. Path.,' Bd. i, p. 46; 'Cellularpathologie,' 4 Aufl., Berlin, 1871, pp. 364, 458.

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* Heidenhain, 'Pflüg. A.,' v, p. 309.

In its pure and unadulterated form the cellular theory of inflammation is, in fact, at present maintained by no one. Neither its founder nor the author who has recently appeared as its enthusiastic champion, Stricker in Vienna,* doubt, so far as I know, the independence of the events taking place in the vessels, and their exemption from all influence on the part of the cells. Nor can it be questioned that the processes connected with the vessels are sufficient to bring about the aggregate phenomena characteristic of inflammation, for Senftleben† has shown that a cornea, the whole of whose corpuscles have been killed and made to disappear by the injection of a few drops of oil of turpentine into the interior chamber, becomes cloudy and swollen, and most densely infiltrated with pus corpuscles, so that, despite the absence of all fixed corneal corpuscles, it presents to the naked eye, and when examined microscopically, a typical picture of most genuine inflammation. This being the state of affairs, the only question that can be debated at present is whether, side by side with the circulatory disturbances, Virchow's so-called nutritive and formative changes of the tissue-cells at all occur in inflammation, and in particular *whether by means of these changes exudation- or pus-corpuscles, arise.* Let me attempt to define my position with regard to this question. It would be preposterous, I think, to expect that the tissue-cells should remain absolutely unaffected and unaltered by the inflammation. Are they not living beings with a metabolism, the details of which are indeed in several respects unknown to us, but which certainly in many of them is a very active one? Would it not be very surprising, therefore, if their structure and chemical constitution were to continue altogether unchanged, though the velocity of the blood-stream through the vessels supplying them has diminished, and they are now bathed by an abundant exudation having anything but normal characters, instead of by a normal transudation of moderate amount. Moreover, the tissue-cells are in many cases directly affected by the causes of inflammation. Ischæmia deprives not only the vessel walls but the tissue-cells of their supply of nutritive fluid, and the same heat which scalds the vessels of a rabbit's ear on plunging it into hot water, equally affects its tissue-cells. On touching the cornea with nitrate of silver, the tissue within and immediately around the corroded portion with the contained cellular elements, will be earlier, and at any rate much more powerfully, influenced than will the vessels in the periphery of the cornea, to which the chemical action of the caustic extends only very gradually, and after considerable attenuation. Accordingly the development of many processes leading to the disorganisation and degeneration of the tissue-cells of an inflamed part is absolutely unavoidable, and cells which have survived the actual onslaught of the exciter of inflammation must very often subsequently succumb to disintegration, necrosis. As has been said, there is nothing remarkable in all this, and the question would hardly be so warmly discussed did it merely involve the explanation of the disintegration of cell-nuclei into small fragments, or the appearance of coarse or fine granules, fat drops, or vacuoles in cells, and the like. But has it really been made out that the changes of the tissue-cells are simply retrogressive? Do not changes of an altogether different kind take place side by side with these, perhaps in certain other cells—changes which, as Virchow called them, are *progressive*, and finally lead to the formation of new cells, pus-corpuscles? An assumption of this kind was not merely permissible, but even enjoined, at a time when the capacity of the pus-corpuscles for locomotion, and especially their emigration, was still unknown. Nothing then appeared more natural than that the pus-cells found anywhere should be the descendants of the tissue-cells of the locality. Since an acquaintance with cell extravasation has become common property, this assumption is no longer necessary, for we now know that prodigious quantities of colourless cells can be furnished by the vessels of an inflamed area. Under these circumstances the question whether, in addition to these, a certain number of pus-corpuscles are produced by the tissue-cells, is as regards the inflammation itself, of really subordinate importance; and it would be difficult to understand why this particular problem should, in the last few years, have stimulated the activity of so large a number of inquirers, were not certain weighty problems of cell-life bound up with it.

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* S. Stricker, 'Studien aus d. Inst. f. exp. Path. in Wien,' 1870, and various papers in the 'Wien. med. Jahrb.' since 1871.

† Senftleben, 'Virch. A.,' lxxii, p. 542.

The decision of this question is, I willingly confess, more difficult than appears at first sight. As late as the seventh decade of this century the matter was simpler; if a pus-corpuscle were met with in an epithelial or other cell, it was unhesitatingly assumed to have arisen *endogenously*, and if two or three were found in a situation where a connective-tissue cell might be expected to be present, as, for example, in the position of a so-called corneal corpuscle, they were spoken of as the descendants of the latter, and were supposed to owe their origin to its division. Improved histological methods make it possible now-a-days to recognise cells where they formerly escaped observation; above all, we know that pus-corpuscles can wander into every part, and, in particular, that they can penetrate into other cells. We accept the *new formation* of a pus-corpuscle as demonstrated, only where we have seen it take place directly under our eyes, or where—and this appears the utmost concession we can make—strict proof can be offered that the pus-corpuscle in question cannot have travelled from some other place. No one has so far succeeded in observing the formation of a pus-corpuscle. The base of a wound of the frog's tongue affords the best opportunity for watching, for hours together, the behaviour of the fixed connective-tissue corpuscles during the simultaneous progress of the circulatory disturbances. The only changes which I and several other subsequent observers have seen in them are the assumption by some of a more strongly granular character, and the rounding off of others by the liquefaction of their processes.* Stricker also failed to observe a solitary instance of division, or other so-called progressive change, during an examination continued for ten hours.†

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* Cohnheim, 'Virch. A.,' xlv, p. 333.

† Stricker, 'Studien,' p. 26.

Moreover the second mode of proof has not so far been attended with success. Böttcher* especially has directed his efforts to this aspect of the question. He has been at pains to produce small circumscribed inflammations of the cornea by very slightly irritating its centre, hoping in this way to avoid any implication of the conjunctival vessels. Pus-corpuscles in small numbers may actually be observed in these small central opacities, and it is very easy to convince oneself that they are not immigrants from the periphery of the cornea. Nevertheless, this result does not prove anything, since pus-corpuscles can quite as readily penetrate the exposed corneal tissue from the conjunctival sac in front of it; and in the conjunctival secretion lymph-corpuscles are, as is well known, invariably present, but more especially after irritating the cornea.†

Though, as we have seen, a new production of pus-corpuscles from fixed tissue-cells has not so far been demonstrated, this failure does not preclude the occurrence in the latter of other *progressive* changes. As a matter of fact, *regenerative* processes occur often enough later on (whenever any of the cells going to form the affected part have perished during the inflammation); and these, as you will hear presently, have their origin in the fixed tissue-elements. But if we disregard such processes, which after all are to a certain extent accidental concomitants of inflammation, the prospect of proving the occurrence of progressive cellular changes, directly induced by the inflammatory irritant, appears doubtful enough. Here, too, the cornea chiefly has been pressed into service. The corneal corpuscles, according to Stricker‡—and, following him, many other authors—become contractile in consequence of the irritation; and some of them are transformed in inflammation into *large contractile multinuclear* protoplasmic masses. Now I will not touch at all on the histological controversy as to whether the corneal corpuscles, *i.e.* the well-known star-shaped figures in the cornea, really represent cells or whether they are merely spaces, as held by Schweigger-Seidel;[*] I prefer to occupy the standpoint of those who have no doubt as to the cellular character of these figures. Even so, it may properly be objected, in opposition to Stricker's view, that the protoplasmic masses in question have arisen out of the pus-corpuscles, presumably through the coalescence of several of them, and have nothing whatever to do with the corneal corpuscles. Yet the contrary has received further support from another author, Walb,[†] who injected carmine into a cornea, without the occurrence of any inflammation worth mentioning, and after a time found *red, carmine-coloured giant-cells;* while immediately after the injection, the star-shaped, corneal corpuscles were those chiefly stained by the carmine. Does not this simple and ingenious experiment plainly speak for the development of giant-cells out of corneal corpuscles, and, by consequence, for a greatly increased growth of the latter, an exquisitely progressive change? I should unconditionally answer in the affirmative, had not Senftleben[‡] shown *that giant-cells, the exact counterparts of these, arise when carmine is injected into the cornea of the dead rabbit, and the cornea introduced into the abdominal cavity of a living one.* Despite every difficulty on *a priori* grounds, it is again (as this remarkable, but invariably successful, experiment shows) *the colourless corpuscles,* which, by penetrating into the dead cornea and undergoing further changes there, give rise to these protoplasmic masses resembling giant-cells; and if they can accomplish this in the dead cornea, one may surely credit them with it in the living. This fact will, I think, make you at all times suspicious; you will be inclined to ask whether the contractile compound corpuscles, into which, according to Popoff[§], the ganglion-cells of the brain become metamorphosed in inflammation, are not also the offspring of extravasated, colourless blood-corpuscles; and you will agree with me, I hope, if I sum up the results of our discussion as follows: *that*—leaving out of account regenerative processes—*pro-*

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* Böttcher, 'Virch. A.,' lviii, p. 362, lxii, p. 569.

† Cohnheim, 'Virch. A.,' xl, p. 65, lxi, p. 289; Key u. Wallis, 'Virch. A.,' lv, p. 296; Talma, Graefe's 'Arch. f. Ophth.,' xviii, Heft 2; Eberth, 'Untersuchungen aus dem pathol. Inst. in Zürich,' Heft 2, p. 1, Heft 3, p. 106.

‡ S. Stricker, 'Studien aus d. Inst. f. exp. Path. in Wien,' 1870, and various papers in the 'Wien. med. Jahrb.' since 1871.

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[*] Schweigger-Seidel, 'Arb. aus d. Leipz. phys. Anst.,' 1869.

[†] Walb, 'Virch. A.,' lxiv, p. 113.

[‡] Senftleben, 'Virch. A.,' lxxii, p. 542.

[§] Popoff, 'Virch. A.,' lxiii, p. 421.

gressive changes in the tissue-cells of an inflamed part are indeed possible, but that *their occurrence has not up to the present been established beyond doubt.*

But we may dispense with all this, if we hold fast the conviction which was directly forced upon us by our experiments and reflections—namely, that inflammation is the expression and consequence of a *molecular alteration in the vessel walls.* By it, adhesion between the vessel wall and the blood, and in consequence friction, is increased; the result is the *retardation of the blood-stream* within the inflamed district. On the other hand, the permeability, the porousness, of the walls is augmented by the molecular change; the result is *an increase of transudation, and of the albuminous contents, as well as the admixture of colourless and red blood-corpuscles with the transuded fluid.* That the frictional resistance in the vessels is actually increased in inflammation, a glance through the microscope most conclusively proves. If no *mechanical* impediment be present, either *in advance of,* or *behind,* the inflamed vascular area; if arteries as well as veins be wide, and thoroughly pervious, and at the same time the blood have preserved its normal constitution, how is a retardation of the blood-stream possible, except as the result of increased frictional resistance on the part of the vessel wall? Moreover, the greater permeability of an inflamed vessel-wall, as compared with a normal one, is also susceptible of direct proof. It was formerly said, indeed, that the vascular coats had become brittle, more readily ruptured; and it was supposed that the occurrence of punctiform hæmorrhages could be referred to this condition.* This, of course, is incorrect, as we now know; the hæmorrhages arise by true diapedesis, and not by rupture of the capillaries. Indeed the internal cohesion of the latter appears to be completely unchanged; they can, without rupturing, sustain during artificial injection the same pressure as normal vessels. On the other hand, the inflamed vessel walls permit, as Winiwarter† has proved, the passage of a colloid liquid—as for example gelatine-solution—under a lower pressure than do the walls of normal vessels; which denotes simply an *increase in their permeability.*

* Küss, 'De la vascularité et de l'inflammation,' Strasburg, 1846.

† Winiwarter, 'Wien. akad. Stzgsb.,' 1873, Bd. lviii, Abth. 3.

Our knowledge is at present too imperfect to allow of our defining more precisely the nature of this alteration of the vessel wall. That anatomical changes—such changes, that is to say, as are recognisable by our optical appliances—should be at the root of it, is obviously unnecessary; and, at any rate, no such changes have so far been demonstrated. For to say nothing of the alleged multiplication of the nuclei, I cannot regard as particularly happy the statements of Jul. Arnold[*] according to which the natural stomata between the endothelial cells dilate, or new stomata and stigmata form in the intercellular cement. The objections raised to the stomata-hypothesis in connection with venous stagnation apply here also; if the corpuscles really passed through such large openings, it would not be possible to conceive why the fluid portion of the blood, the plasma, should not more easily, and at an earlier period, also pass out. Now the fluid of the inflammatory transudation is in no sense plasma, and if we neglect the fibrin, not even serum; in spite of its concentration, it is greatly inferior to the blood serum in point of solid residue. The inflammatory product is a true, genuine *filtrate*; *i. e.* a fluid which has passed through the actual pores of the filter, and not through apertures in it. The process of inflammatory exudation may be best compared to a filtering process. The ordinary filter, the normal vessel wall, permits the passage of only a small quantity of a moderately concentrated fluid; substitute a filter with coarser pores, and not only will more water, but more colloid substance, flow through, —the latter both in solution, and in the shape of formed elements, the blood-corpuscles. For the extravasation of the blood-corpuscles is also a mere process of filtration, as Hering[†] was the first to announce. The exit of the colourless cells does not depend on spontaneous movements, as I myself formerly supposed, and as is, oddly enough, still maintained by Binz[‡] and other writers. For on interrupting the flow in any way, *e. g.* by compressing the principal artery, all further extravasation ceases instantaneously and completely, although previously the most active emigration had been observed in the vessel:—*without pressure no emigration*. On the other hand, it is not a *rise* of pressure that forces the blood-corpuscles through the vessel walls, not even in the case of the red ones. For not only is there no rise but actually a *fall*, in the vessels of an inflamed part; and certainly, if the normal pressure cannot force the blood-corpuscles through healthy vessels, a lower one cannot do so. Indeed, even in vessels whose walls have been altered by inflammation, a rise of pressure may check extravasation, when it coincides with an increase in the velocity of the stream. To this it is to be attributed, I think, that inflammations are wont to run a more favorable course after division of the vaso-motors concerned; as was long since established for the rabbit's ear. And that the milder course is really attributable in these cases to the augmented velocity is taught most beautifully by an inflammation experiment, in which the blood is greatly diluted. If you inject into the v. abdominalis of the frog a 0·6 per cent. solution of common salt, by means of a Pravaz's syringe, the velocity of the blood-stream will be increased exceedingly—a point to be discussed later on. Now lay bare the mesentery, or make a wound in the tongue; and you will find that, though inflammation sets in, a much longer time must elapse before the "pavementing" and the extravasation of the blood-corpuscles occurs, and that the latter is insignificant in amount while the acceleration of the stream continues.*

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[*] J. Arnold, 'Virch. A.,' lviii, pp. 203, 231, lxii, pp. 157, 487, lxvi, p. 77, lxviii, p. 465; Foà, 'Virch. A.,' lxv, p. 284.

[†] Hering, l. c.

[‡] Binz, 'Virch. A.,' lix, p. 293.

But the stomata-hypothesis is also deficient, in that it fails to explain *the hyperæmia* and *the retardation of the stream*, which as you know, set in as far back as the *arteries* of an inflamed part. For the inflammatory change in the vessel wall is of such a nature as to occasion, firstly, atony of the muscular coat, and then, at the same time, an increase of frictional resistance and of permeability. True, there is, in the abstract, nothing to prevent the occurrence of an increase of permeability, as the result of some process or other, without any accompanying augmentation of the frictional resistance; and similarly it is quite conceivable that the latter should in certain circumstances be increased, while the perousness of the vessel walls continues unaltered. But in inflammation everything appears to me to point to a simultaneous and uniform increase of both factors. While the blood continues to flow with increased velocity through the dilated vessels there is no increase of transudation; and, conversely, transudation is most copious when the blood-stream is slowed to such an extent that stagnation is every moment impending. Indeed it is by no means clear whether such an amount of change as causes the death of the vessel walls might not augment their permeability to the most extreme degree possible; since, as we formerly saw, the blood does not penetrate at all into the dead vessels owing to the excessive resistance, while whatever blood is already within them very quickly coagulates, so that all chance of any transudation is for other reasons excluded from the first.

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* Cf. Thoma, 'Virch. A.,' lxii, p. 1.

Such being the state of affiairs, the idea must logically present itself that it is an alteration of substance, a change of a *chemical character*, which is undergone by the vessels in inflammation; and that this induces the characteristic circulatory disturbances. The mode in which J. Arnold* has last formulated his stomata-hypothesis is no longer inconsistent in principle with this view. For he now supposes the cement-substance of the vascular endothelium to be composed of a fluid, or at most tenacious, mass, which in inflammation becomes less coherent (*i. e.* experiences an internal change), and grows to be abnormally permeable. Arnold, accordingly, lays stress exclusively on a change in the cement-substance; and for the reason that, in infusion-experiments with dissolved and corpuscular colouring matters, he has always observed and traced the transit of the latter in the lines of cement alone. To me these experiments, however interesting, appear too inconclusive to justify one in entirely disputing the possibility of a filtration through the endothelial plates. But not to dwell any longer on this point, I am far from oblivious to the fact that the designation I have chosen, "a change of chemical nature," is a very indefinite one; but if it be to-day impossible to define this alteration more precisely, we pathologists should in truth suffer no reproach, in view of the obscurity in which even the physiological process of normal transudation is so far enveloped. No one has up to the present been able to specify the causes on which the different chemical composition of the transudations of various regions depends; no one knows with certainty why the pleural or pericardial vessels yield a transudation so much more concentrated than do those from which the cerebro-spinal fluid is derived. Every day furnishes some new and surprising testimony to the importance of the vessel walls as influencing the course of the vital phenomena, and to the liveliness with which they react to all sorts of influences. That by their action the vascular lumen can be narrowed or dilated is a fact with which we have long ago familiarised ourselves; and we have learned to reckon with it in physiology and pathology. Since, however, it has been shown in Ludwig's laboratory,[*] *that a concentrated lymph is formed in curarised animals,* should not our attention be directed by this discovery to an altogether different side of the relations existing between vessel walls and blood-stream? When, on injecting a solution of curare into a vein of a dog, we immediately see the skin become reddened, we experience no particular surprise; for we are accustomed to ascribe to curare a paralysing or, too, an exciting action on the vaso-motor nerves. The poison cannot, it is true, influence the transudation by this, its well known capacity; but why should it not be capable of acting on other constituent parts of the vessel wall as well as on the nerves of its musculature—why not directly upon such parts as bring about transudation, even though these be still unknown to us? It is possible that nerves are the agents here also, or at least that they may influence the process of transudation. This has long been established for a number of secretions, and more recently, by Ostroumoff's experiment, for the vessels of the tongue (cf. p. 141). There are some additional facts which speak very forcibly in favour of a capacity in the nerves to influence other properties of the vessel wall as well as its contractile power, namely the rapid development of œdema in the paralysed limbs, so often observed in acute myelitis;[†] and the discovery of Gergens[‡] that the blood-vessels of frogs allow a larger quantity of fluid, and even particles of a granular colouring matter, to permeate through them after destruction of the spinal cord. Who would to-day hazard an opinion as to whether a specific nervous apparatus of this kind, situated in the vessel wall itself, may or may not co-operate in inflammation also? Besides, we have not to do here with anything of a novel character, of a nature absolutely foreign, on whose appearance the inflammatory transudation is *suddenly* yielded. The case resembles rather the contrast between health and disease; between the normal circulation and the inflammatory circulatory disturbance there are all imaginable gradations. Not only does the quantity and concentration of the fluid-transudation show such gradual increases that it is altogether arbitrary whether certain degrees should be referred to inflammation, or recognised as within the limits of health; the extravasation of the corpuscular elements of the blood presents the like gradations. In certain early, embryonic stages of animal development, the emigration of colourless blood-corpuscles appears to be a perfectly regular and, without doubt, important process.* In the great majority of the areas and regions of the fully developed and completely grown individual no such importance attaches to it; but this of course in no way precludes the possibility that an individual white corpuscle may now and then transude somewhere; still less does it negative the idea that the vessels of certain organs may from the first be so contrived as to allow of a physiological transudation of corpuscles. We shall not be over rash, I think, if we make such an assumption in the case of the lymphatic glands, the spleen, the medulla of bone, and also the liver; while as regards the red corpuscles we have, in the circumstance that they are almost constantly met with in the chyle-vessels of the mesentery during digestion, an unmistakable sign that blood-corpuscles may extravasate from the capillaries of the intestinal mucous membrane during the *physiological* variations of the circulation. But with affairs in this state, it seems to me that any endeavour to set up an exhaustive hypothesis as to the essence of the inflammatory

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* Cf. in particular Arnold, 'Virch. A.,' lxvi, p. 77.

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[*] Paschutin, 'Ber. d. Leipz. Ges. d. Wissen. Math.,' Phys. Kl., 21—2, 1873.

[†] Leyden, 'Klinik der Rückenmarkskrankheiten,' Bd. ii, p. 173.

[‡] Gergens, 'Pflüg. A.,' xiii, p. 591. On repeating these experiments in

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the institute here Rütimeyer was unable to determine the existence of differences so great as those found by G., 'A. f. exp. Path.,' xiv, p. 393.

* Recklinghausen, in Stricker's 'Gewebelehre,' p. 249.

changes in the vessel walls would not merely be useless, but even calculated to render the future solution of the riddle more difficult.

From the standpoint so arrived at, the question as to the *causes of inflammation* may also, I think, be most simply settled. For every agency *by which the chemical constitution of the vessel walls is at all altered,* and which, on the other hand, is not so powerful as to bring about the death of the vessels, must be calculated to produce an inflammation of the part of the body concerned. Accordingly, as I may at once remark, a classification of inflammation from an etiological point of view cannot be exhaustive. It is, indeed, an old, everyday experience that different causes may produce the same effect—an experience which was fully borne out by our introductory experiments. No *dissimilarity in the process* arises out of this diversity in the causative noxæ. A meningitis of epidemic origin is the same process as a meningitis following the rupture of an abscess of the brain or an injury to the skull; and an epidemic erysipelas does not differ in kind from one caused by the prick of a poisonous insect or a burn of slight degree. Only graduated differences exist, and these depend on the intensity of the noxa at work, not on the essential nature of the process. But even were we to limit ourselves to establishing an only partially exhaustive, so to speak, *casuistical,* etiology of inflammation, this problem would probably be impossible of solution. For it is much easier, as you will doubtless perceive, to say under what circumstances any agency does not bring about inflammation, or ceases to bring it about, than to formulate those characteristic peculiarities which an agency must possess in order to cause inflammation. One must be content with the statement that every foreign agency outside the limits of physiological conditions, between which and the vessels there is action and reaction for a sufficient period, may constitute a cause of inflammation, though this, it is true, amounts, as you will notice, to nothing more than a negative definition.

Although, with matters in this state, we cannot deceive ourselves into believing that the domain of the etiology of inflammation is limited, and must admit that new causes may daily originate and be discovered, it will nevertheless appear to you advantageous to discuss briefly such of them at least as are more commonly met with, and are therefore of greater practical importance. The varieties of inflammation, with which we became acquainted in our introductory experiments were,—in addition to protracted ischæmia, which in the natural course of things can perhaps hardly occur,—two in number, namely, inflammation due to the action of extremes of temperature, *i. e.* inflammation from *scalding* or *freezing;* and the form due to chemical action which we commonly call *corrosion*, the processes themselves being known as *toxic inflammations*. To this category belong the direct corrosions, whether caused by the application of a caustic or by the inoculation of a poisonous substance, by the bite of an insect, for example: other examples are the gastritis following the consumption of large quantities of alcohol or other poison, and the myositis due to the entrance of trichini into the muscles. In the same category must be placed those processes in which certain injurious substances, having become incorporated in the organism or arisen within it, either accumulate in definite localities or are there excreted, and in this way prove most obnoxious to the vessels of the part in question; examples are afforded by stomatitis after the use of mercury, catarrh after iodine, nephritis after cantharides, as well as by arthritis in the gouty. But the domain of the toxic inflammation in a broad sense, *i. e.* of inflammations called forth by chemical action on the vessels of a part, is much more extensive still. For unquestionably to it belong all inflammations caused by abnormal changes in the composition of fluids or tissues in contact, or coming into contact, with the vessels. We must include here the stomatitis or gastritis due to abnormal fermentative decomposition of the constituents of the food, which is known to be especially frequent in children at the breast; the peritonitis following perforation of the intestine with the escape of decomposing and putrid matters into the peritoneal cavity; the so-called metastatic abscesses which are developed round puriform emboli; and, above all, the inflammations occurring around *dead parts*. For, around the latter, inflammation never fails to appear, although its intensity is liable to vary extremely. Should any of you, however, imagine that this factor plays a subordinate part in the organism and scarcely deserves to be mentioned amongst the most important causes of inflammation, I believe that, without anticipating here the more minute discussion of local necrosis to follow later, I can refer you to a few points, which seem to me well calculated to place the importance and frequency of local death of the tissues in a proper light. I do not desire to remind you how frequently we have already met with necrosis following local disturbances of the circulation, for at present the fact *that the vast majority of traumata must necessarily bring in their train a localised death, of greater or less extent, is much more deserving of consideration.* When a foreign body enters an organ, not only will the tissues through which it has forced its way mortify, but also the layer of tissue immediately surrounding the spot where it is lodged. If you make a cut or tear through any part of the body, the portions coming into direct contact with the cutting instrument will certainly undergo mortification. If you crush any part, or apply force with a blunt instrument, either the effect will not exceed the limits imposed by the elasticity of the tissue, and then the violence is perfectly harmless, or some minute portions are injured beyond recovery and perish. The same applies in a still greater measure to the combination of concussion or crushing with laceration, as in ordinary fractures of bone. Lastly, when a part of the body is deprived of its protective coverings, it is hardly possible for the uppermost layer to withstand the unnatural influences to which it is exposed; it dies—a fact which has been directly proved in the case of especially sensitive tissues, as, for example, the striped muscles. The extent of the necrosis following these various traumata depends on several secondary circumstances. The tissue surrounding a red-hot foreign body will perish to a greater depth than would be the case with an unheated one; and while a severe bruise can cause such mortification of the affected tissue that it is subsequently cast off *in toto*, a perfectly sharp instrument may perhaps leave such a minimal zone of necrosis after it that our methods fail to detect its presence, although no one can reasonably doubt that cells which have been cut in two must perish. But however the necrosis is called forth—and you will become acquainted later with other completely heterogeneous causes —it is certain that under all circumstances *the dead mass excites in the neighbouring tissues and cells abnormal chemical changes*, which sooner or later extend *as far as the nearest vessels.* It is possible, at most, that in small circumscribed necroses of non-vascular tissues, as, for example, the cornea, the process may remain confined to the non-vascular district, and may never reach the vessels. But leaving such exceptional cases out of account, inflammation, as stated, invariably sets in around necrotic parts. Whether, however, it is limited in extent and severity, or develops considerable intensity, depends in the first place, obviously, on the dimensions of the primary necrosis, and, in the second place and chiefly, *on the appearance or non-appearance* in the dead mass *of yet other especially energetic processes of decomposition.* Here the most important factor is the presence of lowly organisms, of *schizomycetes.*

On another occasion, when discussing the puriform softening of thrombi, I called attention to the possibility that bacterial germs may arrive in the human body, and develop there just as in other organic substrata. I, however, at once proceeded to lay stress on the fact that our organism is threatened only by such of the schizomycetes as can maintain life and retain the capacity for development in presence of the metabolism of the human body. For this reason the true bacteria of putrefaction are innocuous to the healthy animal; nevertheless this innocuousness is quite compatible with the facts that they settle and go on developing in portions of the living organism which have perished, and here bring about the chemical effects characteristic of them. Hence putridity and putrefactive decomposition are sometimes observed to occur in tissues which have undergone traumatic necrosis; but though I am far from denying this, and readily admit that very severe inflammations are developed under the influence of such putrefaction, I hold that the putrefactive organisms play in traumatic inflammation, just as in the softening of thrombi, an unimportant part. For micrococci settle in necrotic portions of tissues in man very much more frequently than does bacterium termo; they certainly do not

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excite putrefaction, but are never absent where it is going on, and are thus no less ubiquitous than the bacterium termo. Amongst the micrococci also there are certainly different species, though, with the optical appliances now at our command, we are not always able to distinguish them; amongst them are undoubtedly some which are capable of sustaining the competition of the vital metabolism. But though the micrococci are not so exclusively confined to dead tissues, there is no doubt that these constitute the most favorable soil imaginable for their settlement and multiplication. This is shown most strikingly both by experiment and experience. An extravasation of blood in the subcutaneous cellular tissue, or in the abdominal cavity is in itself absolutely innocuous, and is never subject to profound decomposition. It has been proved, on the other hand, by various experimenters that fluid containing micrococci may unhesitatingly be injected under the skin or into the abdominal cavity, of a rabbit, without any pathological effect whatever. But to the extreme danger attending the simultaneous presence of micrococci and blood, or bloody transudation, in the abdominal cavity, the attention of surgeons has only a short time since been called by Wegner,* who pointed out the constant occurrence, under such circumstances, of decomposition of the fluid in the abdominal cavity. For the decomposition of materials contained in this cavity never fails to excite severe peritonitis; while the extravasation, if not decomposed, undergoes simple resorption, though it may be slowly. Similarly, large quantities of an indifferent fluid, containing micrococci and bacteria, may be injected into the bladder without any reaction ensuing, because a soil for the further development of the bacteria is wanting, and they are removed at the next micturition. But as soon as you introduce precisely the same micrococci by means of an imperfectly cleansed catheter into a bladder in which the urine has been stagnating, the stagnant urine at once begins to undergo ammoniacal fermentation. Like the alkaline fermentation in the bladder, there take place in the tissues, *pari passu* with the growth of the micrococci, those deeper, chemical changes to which the organism responds by inflammation in its more violent forms.

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* Wegner, 'Langenbeck's A.,' xx, p. 51.

The difference in the course of inflammations around dead parts will, in the light of these circumstances, be understood without further explanation. If the organism succeeds in guarding against the entrance of bacterial germs into the necrotic portion, there is no very active decomposition, and the dead tissue passes through certain harmless changes, to which we shall have to turn our attention later—changes which are not at all calculated to produce much effect on the vessels of the neighbourhood, if for no other reason, because they are slowly developed. Hence it is that we rarely see anything more than a very slight inflammation around an embolic infarct of the kidney or the spleen, while decomposition is commoner in hæmorrhagic infarcts of the lung, and a demarcative suppuration ending in sloughing is more frequently established around them. But herein is to be found a key to the interpretation of the course taken by the so-called *traumatic* inflammations. You now know why it is that the inflammation attending a simple fracture does not exceed certain moderate limits, and why after a so-called compound fracture, *i. e.* one associated with a wound of the skin, it often proves so dangerous. You know why the chances of healing are so much more favorable in subcutaneous than in open wounds. It is not, as was formerly supposed, the exclusion of air that makes subcutaneous wounds so harmless, for you may force considerable quantities of ordinary air under the skin of a rabbit till the body of the animal becomes enormously distended, and may even repeat the experiment on several successive days, after having on each occasion previously removed the unresorbed air by pressure, without phlegmonous inflammation setting in. Moreover, Wegner* conducted air for many hours together through the abdominal cavity, in dogs and rabbits, without a trace of consecutive peritonitis. It is the bacterial germs which, meeting with a favorable soil in those portions of the tissue that have mortified in consequence of the trauma, or in the secretions of wounds, rapidly multiply there, and call forth energetic decompositions, which again considerably increase the intensity of the inflammation.

You see I am not at all disposed to under-estimate the importance of the schizomycetes in traumatic inflammations; on the contrary, I even hold that the occasional severity of their course is in great part attributable to the action of bacteria. Any more far-reaching conclusion is not, in my opinion, borne out by experience; and in particular I regard the attempt made by some, amongst whom Hueter[*] has been specially active, to embrace all the traumatic inflammations under the one head of bacterial action, as absolutely futile. This view was, in the first instance, an inference from an experiment by Zahn,[†] who observed that, on laying bare the mesentery of a frog, inflammation failed to set in, when care was taken that the air to which this membrane was exposed should be free from germs. Hueter further sought to establish this view on a firm basis by a number of experimental investigations carried out by his scholars.[‡] In these the attempt was made to prove that subcutaneous and aseptic injections of solutions of nitrate of silver and of chloride of zinc, as well as cauterisation with a red-hot metal, cause no kind of inflammation whatever, and that inflammatory changes are only set up, when, simultaneously with the exciter of inflammation, air get access into and around the affected tissue. The success attending the Listerian method of operating and bandaging which, it is claimed, preserves wounds from all inflammation, has moreover been appealed to and specially dwelt on in support of the view. Now with regard to the experiment of Zahn, it is difficult to reconcile the alleged result with the fact that frogs, unlike the higher animals, do not usually react to the application of putrid fluids or solid particles by violent inflammation; and at any rate, on a repetition of Zahn's experiment in my laboratory in Breslau, Lassar failed to get the same result. He found on the contrary that inflammation could never be prevented from setting in in the mesentery drawn out of the abdominal cavity, even when the greatest possible precautions were taken. The process develops in a strictly typical way; and we shall make no mistake, if we regard the circumstance that, after the mesentery is removed from the abdominal cavity, its vessels are placed in conditions utterly different to the normal, as being the actual cause of the inflammation; in the production of which it is not improbable that necrotic processes involving the surface of the mesentery also participate. Accordingly, Zahn having, it would seem, been deceived by an accident, as is easy to understand when we remember the great differences in the time taken by the mesentery experiment to run its course, I must also most decidedly dispute the statement that inflammation is altogether absent in the neighbourhood of a subcutaneous eschar, caused by the action of corrosives or by gangrene. This is just as far from being true here as it is in the case of an embolic infarct of the spleen or kidney. Inflammation is present, but may be very trifling in character, so that the cardinal symptoms, generally so conspicuous, may not be perceptible through the skin: but if a *microscopical* examination be properly carried out, the *rubor* and *tumor*, *i. e.* the zone of hyperæmic vessels and of extravasated blood-corpuscles cannot escape detection. When Listerian dressings are employed, the circulatory disturbances characteristic of inflammation are also never absent; although here too the inflammation is a feeble and very superficial one. It must necessarily be so, because the tissue elements lying a little deeper are all of them protected against destruction by the antiseptic procedure and the conditions most favorable to regeneration therefore secured. The same holds good of *subcutaneous wounds:* the formation of callus in a fracture, of the cicatrix after subcutaneous tenotomy depends, as will presently be explained, essentially on *regenerative* processes; nevertheless it would be a serious error were one to claim that no inflammatory hyperæmia and inflammatory exudation take place here. For that which is absent in subcutaneous wounds, and which, in open ones, is kept at a distance by antiseptic treatment, *is not inflammation, but only that form of it in which pus is produced.* If these two things, inflammation *per se* and purulent inflammation, be carefully kept distinct, the difference of opinion between Hueter and his followers and ourselves, at once becomes apparent. We regard purulent inflammation as but one form of the process, with whose conditions we shall presently have to occupy ourselves more closely; while Hueter, on the contrary, places all other terminations in the background, and hardly shrinks from the proposition, "that genuine inflammation is characterised by a tendency to form pus." Such a standpoint may perhaps be intelligible to a surgeon, whose study of inflammation is based exclusively, or chiefly, on the traumatic form; especially when, like Hueter, he is disposed, in accordance with an old definition, to maintain the *character of danger* as necessary to inflammation. But an addition to our knowledge of the inflammatory process can hardly accrue from a limitation of this kind. In direct opposition to Hueter's notion of the unity of the inflammatory process, his monadistic theory, we believe that we have gained for ourselves in various directions such an insight into inflammation as could not otherwise have been attained, by employing agencies of very different kinds and endeavouring to acquire experience as to their mode of operation—experience which has, in truth, lost none of its importance through the fact that Hueter has, I regret to say, distorted it to suit his monad-theory. Moreover, none but those who are determined to close their eyes to the facts of internal medicine, and of pathological anatomy, could accept a doctrine which insists that the termination in the formation of pus is the indispensable criterion of every genuine inflammation. Is there not, amongst those very inflammations whose dependence on bacteria cannot reasonably be doubted, namely, the *infective* inflammations next to be discussed, a considerable number whose products never present the characters of pus?

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* Wegner, ibid.

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[*] C. Hueter, 'Allgemeine Chirurgie,' Leipzig, 1878, p. 8; 'Deutsche Zeitschr. f. Chir.,' ix, p. 401; 'Grundriss d. Chir.,' Leipzig, 1880, p. 1.

[†] Zahn, 'Zur Lehre v. d. Entzündung und Eiterung,' I.-D. Bern, 1871.

[‡] Dembeczak,' Experimentalstudien über parenchymatöse Injectionen von Arg. nitricum,' I.-D. Greifswald, 1876; Rausche, 'Experimentalstudien über parenchymatöse Injectionen von Chlorzink, I.-D. Greifswald, 1877; Hallbauer, 'D. Zeitschr. f. Chir.,' ix, p. 381.

This brings us at once to the so-called *infective* inflammations. By the term *infective diseases* we understand (passing over non-essential characters), such diseases as arise from the action of a poison or *virus*—a virus which is not always and everywhere present, *but is only produced by certain similarly diseased individuals, or in certain localities, or at certain seasons.* The virus is specially distinguished as a *contagium* or as a *miasma*. By the first is to be understood a poison which is developed only in or upon individuals who are already diseased, or, as Pettenkofer* terms it, *endogenously;* while the name miasma is applied to a virus which is produced in the soil, in the atmosphere, or in water, in any case *externally to a diseased organism, i. e. exogenously.* Accordingly contagious diseases can only be conveyed from man to man, or from animals to man, or *vice versâ;* while miasmatic diseases attack individuals who have not come into contact with persons similarly diseased. Examples of purely contagious diseases are afforded by *measles, scarlet fever, whooping-cough, smallpox, typhus, relapsing fever, syphilis;* purely miasmatic are the *malarial diseases,* and above all *intermittent fever.* Measles may be acquired by contact with an affected patient without any reference to place; with a person suffering from intermittent fever, you may on the contrary associate with impunity, but may take the disease in a malarial district without so much as having seen a case. But this distinction in the modes of infection does not apply to all infective diseases. Thus, in *anthrax* we have a malady which is highly contagious, and which in man never occurs except when acquired from animals the subjects of it. But in the case of the animals themselves, it seems to develop spontaneously in a particular locality, and in the absence of contact with other infected animals; it is then derived in all cases probably from the soil, and thus resembles a true miasma. In the opinion of most veterinary surgeons the same may be said of glanders, though by some it is looked on as contagious. Then there are a number of diseases, in which direct infection by personal contact with the patient or his effects does not occur, and yet which never attack anyone without having been first introduced into the locality by individuals. *Cholera* has never broken out in a town except on the arrival of a cholera patient, and yet no cholera patient has ever yet directly infected a healthy individual. The term *miasmatic-contagious* may be appropriately applied to this class of diseases, which, in addition to those just mentioned, includes *typhoid, yellow fever* and *epidemic dysentery;* yet this designation is itself striking testimony that the current classification of infective diseases does not go to the root of the matter. Moreover the group of miasmatic-contagious diseases is anything but small; for one must *nolens volens* make up one's mind to include several other infective maladies, of which it is not possible at present to say either that they are purely contagious or purely miasmatic—for example, *cerebrospinal meningitis*, *erysipelas*, *mumps*, *influenza*, *rheumatic fever*, and true *croupous pneumonia*.

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* v. Pettenkofer, 'Verbreitungsart d. Cholera,' München, 1855; 'Hauptbericht über d. Choleraepidemie in Baiern, 1854,' München, 1856. With the passage immediately following, cf. the highly interesting article by Klebs on "Ansteckende Krankheiten," in Eulenburg's 'Real-Encyclopädie.'

The mention of these various diseases will have given you some notion of the extremely diversified characters presented by the class. In fact it is these very maladies—which from their nature are disposed to attack simultaneously a large number of individuals in the same neighbourhood, to appear as we say, *epidemically*—that present the most manifold and complicated grouping of symptoms, the detailed description of which is of course the office of special pathology. Their chief interest for us at present is the fact that in many of them *inflammatory processes* play an important part. Erysipelas and epidemic meningitis are such thoroughly typical inflammations that the results of an anatomical examination are not, in themselves, sufficient for the establishment of a differential diagnosis between these and other inflammations of the skin or pia of non-infective origin. So perfectly do influenza and pneumonia resemble in their course and behaviour the ordinary inflammations of the same regions that doubts as to the infective nature of the two diseases still continue to be raised by some. Lastly, gonorrhœa and contagious blenorrhœa of the conjunctiva are typical examples of purulent inflammation of a mucous membrane. But even where the chief characters of the particular infective disease are essentially different from those of inflammation, it is nothing uncommon for inflammatory processes to supervene during the course of the malady. Thus abscesses form in pyæmia and in glanders; and in syphilis various acute and chronic inflammations are developed. You see we have ample reasons for asking what is the factor on which the infective inflammations depend, or—to employ language adapted to our own standpoint—*by what agency are the vessel walls of certain organs affected in infective diseases?*

On formulating the question in this way it immediately becomes apparent, I think, that the agent cannot be a virus which circulates *dissolved* in the juices of the body. For how could a poison in solution affect only the vessels of particular districts; especially since the affected regions are not always those into which it is in the first instance absorbed or from which it is afterwards excreted? Add to this further a second circumstance of importance: *the poisons of the infective inflammations,*like those of infective diseases generally, *are capable of reproducing themselves and of multiplying almost indefinitely.* Just as from one drop of the pus of cow-pock hundreds and thousands of human beings may be successfully vaccinated in succession, or in other words, infected, so it is precisely with the infection of measles or scarlet fever, of gonorrhœa, syphilis, or glanders. What kind of dissolved substance could possess a capacity so totally foreign to chemical bodies generally?

Now, if the poison is not in solution it must enter the organism, or distribute itself throughout it, in corpuscular form; and on proceeding to draw the conclusions which directly follow from its reproductive capacity, you will yourselves, I think, hit upon the hypothesis that *living organised beings, lowly organisms,* produce the infective diseases. This is in fact the hypothesis at present most widely accepted and most strongly supported—an hypothesis which under the title of *contagium vivum s. animatum* was long ago maintained by a number of eminent authorities,[*] but which subsequently fell into general disrepute. The justice of some such view could not be more strikingly shown than by the history of *trichinosis.* Here we find a disease appearing at intervals epidemically, sometimes with murderous severity, and having a very typical and specific set of symptoms—a disease which was formerly unhesitatingly assumed to be markedly miasmatic. We now know that the symptoms are produced by trichini; *i. e.* by living highly organised beings, which are conveyed from animal to animal, and thence to human beings, and which establish themselves in the muscles of the infected individual, where they give rise to violent inflammation. In this instance we are accurately acquainted with the development of the infective organism; we know, too, the mode of its dissemination—from the rat to the swine, from the swine to the human being, and we are acquainted, moreover, with the path by which it is disseminated. But is the entire process therefore less of an infection? True we do not now class trichinosis with the infective diseases, but with the parasitic; yet is not our experience here calculated to spur us on to seek a similar explanation for those diseases which are still known as infective?

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[*] J. Henle, 'Handb. d. rat. Pathologie,' Bd. ii, Abth. 2, p. 457; 'Pathologische Untersuchungen,' 1840. Cf. the introductions to Griesinger's u. Liebermeister's "Infectionskrankheiten" in the 'Handbücher' of Virchow u. Ziemssen.

If in these it were simply a question of the existence of such highly organised and palpable beings as those true worms, the trichini, we need not, most assuredly, have waited till our own day for the discovery of parasitic organisms in the infective diseases. But the experiences we have had in connection with the puriform softening of thrombi, as well as a few moments since when tracing the history of traumatic inflammation, indicate unequivocally that for our purpose we must turn to much lower organisms belonging to the great family of the *schizomycetes*. During the last ten years the task of discovering the bacteria proper to the different infective diseases, and of demonstrating the dependence of the particular diseases on them, has been attacked with great activity from various sides; nor has success failed to attend these efforts. I should like first of all to direct your attention to a very remarkable investigation belonging to this period. This investigation has cast such a flood of light on one of the most dangerous of diseases that the result has been a wonderful advance in our understanding of all analogous processes. Since the discovery of glass-clear, motionless, rod-shaped bodies, so-called bacteria or bacilli, in the blood of animals dying of *anthrax*, many attempts have been made to show that these rods are the cause, the contagium, of the disease; and in particular Davaine, one of the discoverers of the bacteria, has sought to prove by inoculations that the potency of the blood, &c., to produce this disease is dependent on their presence in it.* But though his experiments for the most part appeared very convincing, and despite the striking fact that the blood of pregnant animals, affected with the disease, and containing the rods, was infective, while the blood of the fœtus, being free from them, was non-infective, his results were not altogether confirmed by other experimenters. They were unable to convince themselves that, after successful inoculation with blood containing the bacilli, the organisms could always again be demonstrated in the blood of the infected animal; notwithstanding which they found the blood to be active. But above all it was objected to Davaine's hypothesis, and with good reason apparently, that anthrax, as already stated, is undoubtedly connected with a soil having certain characters; so that it is endemic in particular localities and associated with a damp soil. Now all these doubts have been suddenly dispelled by the investigation already alluded to, which was carried out by Koch.* Koch first of all determined the mode of development of the *Bacillus anthracis*, as follows. The rods multiply with extraordinary rapidity in the blood and juices of the living animal by undergoing elongation and then dividing transversely. In the blood of the dead animal, or in a suitable nutrient liquid, the bacilli, if supplied with air, and the temperature be kept within certain limits, grow into *very long unbranched threads* which produce within themselves single rows of spores and afterwards disintegrate; *so that now the spores become free.* Finally these spores *germinate*, and are *directly developed*, in presence of air, and with a suitable nutrient liquid and a certain temperature, *into the original bacilli.* Koch further ascertained that the bacilli themselves are not resisting structures, but, whether supplied with moisture or not, perish after a short time, at furthest a few weeks; and that, on the contrary, *the spores retain their germinative capacity for an extraordinarily long period under circumstances apparently the most unfavorable.* A liquid containing spores infects, we may venture to say, under all circumstances; while one containing rods is infective only when

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* Davaine, 'Compt. rend.,' 1863, Bd. lvii, pp. 220, 321, 386; 'Mém. d.

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l. soc. d. biolog.,' 1865, v, p. 193; Brauell, 'Virch. A.,' xi, p. 132, xiv, p. 432, xxxvi, p. 292; Bollinger, 'Med. Ctbl.,' 1872, No. 27. In Ziemssen's 'Hdb. d. spec. Path.,' iii, p. 447.

* Koch in F. Cohn's 'Beitr. z. Biologie d. Pflanzen,' Bd. ii, Heft 2, p. 277.

these bodies are capable of development and can produce spores, a distinction which Koch has determined by the most careful comparative examinations. These few short sentences, which Pasteur* confirms in all essential points, and has supplemented in only a few really unimportant, and, perhaps still doubtful, particulars, seem to me to contain a perfect solution of the riddle. Anthrax may be directly communicated by the juices of diseased animals containing the rods—*hence the contagiousness;* yet if this were the sole danger, the malady would certainly soon die out in a district, since the rods do not long retain their virulence. But the bacilli contained in the blood of the animals that have fallen a prey to the disease and been buried a short distance below the surface of the moist soil give rise to spores, which retain their germinative capacity for an extraordinarily long time, and under the most varying meteorological conditions. Now, when these gain admission through a wound of the skin into the fluids of an animal, they rapidly develop into rods and cause anthrax; which accordingly is actually derived from the soil, *i. e.* originates in *a miasma.*

I could not deny myself the pleasure of going somewhat minutely into the history of the contagium of anthrax, because here for the first time we see how a well-planned investigation may result in the referring of apparently obscure processes to known biological laws. The success of this attempt to clear up the natural history of an infective disease belonging to the miasmatic-contagious group—to that group which seemed to present the greatest difficulties—appears to me to justify a well-founded hope that a similar effort will in the remaining diseases be still more probably successful, especially in the less complicated purely contagious or purely miasmatic affections. For we cannot so far congratulate ourselves on having solved in the same complete manner the problems presented by any one of the other infective diseases. We are in possession, it is true, of a large number of facts which go to show *the constant presence of certain forms of schizomycetes in particular infective diseases.* I may mention the spirilla of relapsing fever discovered by Obermeier*—delicate threads, which are constantly found during the paroxysm circulating in the blood in innumerable multitudes but which disappear during the remission, only to reappear in equal numbers at the next relapse; further the bacilli of enteric fever found by Klebs† and Eberth;‡ the bacilli of leprosy demonstrated by Neisser;§ the bacilli of malaria detected by Klebs and Tommasi-Crudeli;‖ the micrococci of erysipelas and of endocarditis; besides many other micro-organisms occurring in the infective diseases both of men and animals. Klebs endeavoured to bring forward positive proofs that the bacteria themselves, and not any of the substances simultaneously present in solution, are really the active principle of the infection. For this purpose he employed earthenware filters, by means of which he succeeded in securing the bacilli of anthrax and the septic micrococci free from the surrounding fluid, and in thus rendering the latter innocuous.¶ Klebs did not neglect to follow the botanical history of some of the pathogenic bacteria by carrying out numerous and troublesome cultivations; yet these researches have not received that unqualified recognition at the hands of his fellow scientists which would entitle the results to rank as undoubted additions to our knowledge. What I have thus briefly laid before you is, you will notice, only a small fraction of that which has been added to the literature of this subject during the last ten years; in particular you will not be able from these notes to get more than a very imperfect conception of the fulness and extent of Klebs' investigations. For though some may not always agree with him in matters of detail, they will not dispute the great and lasting service he has done to science

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* Pasteur, 'Bull. de l'acad. de méd.,' 1879, pp. 1063, 1222; 'Compt. rend.,' xci, p. 455.

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[*] Obermeier, 'Med. Ctbl.,' 1873, p. 145; 'Berl. klin. Woch.,' 1873, p. 391; Weigert, ibid., 1873, p. 589; 'Verh. d. schles. Ges. f. vaterl. Cult.,' 1874, p. 56; 'Deutsche med. Wochenschr.,' 1876, Nos. 40, 41; Motschutkoffsky, 'Med. Ctbl.,' 1876, p. 193.

[†] Klebs, 'A. f. exper. Path.,' xii, p. 231, xiii, p. 381.

[‡] Eberth, 'Virch. A.,' lxxxi, p. 58, lxxxiii, p. 486.

[§] Neisser, 'Bresl. ärztl. Zeitschr.,' 1879, Nos. 20, 21; 'Virch. A.,' lxxxiv, p. 514.

[‖] Klebs u. Tommasi-Crudeli, 'A. f. exp. Pathol.,' xi, pp. 122, 311; 'Mem. della reale Academ. dei Lincei,' 1879.

[¶] Klebs, 'Arb. aus d. Berner path. Inst.,' 1871–72, p. 130.

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by holding high the flag of the parasitic theory of infective diseases, with unwearied energy, disturbed neither by indifference nor by unjustifiable attacks; so that he perhaps more than any other has helped to secure for it the victory.[*] Still I cannot conduct you over the whole of this department; and for the establishment of the principle, with which we are here alone concerned, what has already been said appears to me sufficient.

Perhaps it is hardly advisable even to study and analyse the schizomycetes observed in the different varieties of infective diseases with respect to the minutiæ of their form! At least it seems as if a certain repugnance to such studies were the natural consequence of the opinion of those authors, who, following Nägeli, refuse to recognise specific characters in the pathogenic bacteria, and with him conceive that the same species may assume in the course of generations various forms, alternating with one another and morphologically and physiologically dissimilar. By questions like this the parasitic theory of infective diseases is evidently itself uninfluenced, yet the subject is too important to allow of our passing over it in silence. From the standpoint of practical medicine hardly anyone, so far as I can judge, will be much in favour of the theory of the mutability of pathogenic organisms, for if anything is established, it appears to be *the*, so to speak, *distinct individuality of the different infective diseases.* That particular epidemics of typhus or diphtheria differ in severity, and in many other traits, that several of the infective diseases may even have undergone a modification of character in some one or other respect during the course of tens and hundreds of years cannot, of course, be denied, but it is absolutely unprecedented that a disease should change its essential properties or become transformed into another. No trustworthy observation exists to show that anything but measles has ever been communicated by infection from a patient ill with this disease, or anything but smallpox from a smallpox patient; and just as little does all that has been reported of a reciprocity of infection between typhoid and typhus, and of possible transitions from one disease to the other, stand the test of a dispassionate examination. Such being the state of affairs, you will only accept the doctrine of the mutability of the pathogenic bacteria when very convincing proofs, either of a morphological, or, still better, a physiological character, are produced in support of it. Now, as a matter of fact, Buchner* supposed he had afforded such a proof, and announced that by prolonged cultivation he had transformed the bacilli of anthrax into morphologically identical, but pathogenetically completely ineffective, hay bacilli,† and these into the bacilli of anthrax; without doubt a far-reaching and important experiment, provided only it were better accredited! Meanwhile I cannot suppress a fear that Buchner failed, despite all his care, in protecting his cultures from contamination with other bacterial germs, and at any rate the attempts of other practised and trustworthy experimenters to effect the transformation have up to the present been utterly unsuccessful, although all the precautions advised by Buchner were observed by them. More than this,—we are in possession of facts, gathered in this very domain of experiment, which are so little calculated to favour the transmutability of the pathogenic bacteria, that Koch‡ was able, on the strength of them, to devise an excellent method for obtaining pure cultivations of individual forms of the schizomycetes. On introducing a certain quantity of a putrid fluid obtained from any material he happened to select, into mice or rabbits, one out of the many bacteria contained in the fluid soon began to predominate, and with it was developed a certain wound-fever. This predominant form was characterised either by the shape and size of the individual bacteria, or by their mutual arrangement and distribution, and if another animal of the same species was inoculated from the diseased one, *no other form of schizomycetes was at any time developed, while the wound-*

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[*] In addition to the writings of Klebs, already referred to, cf. 'D. Ursache der Infectionskrankheiten, Corresp.-Bl. der Schweizer Aerzte,' 1871, No. 9; 'Verhdl. d. Wurzb. phys.-med. Ges.,' N. F., Bd. vi, p. 5; 'Arb. aus d. Berner path. Inst.,' 1873; 'Beitr. z. path. Anat. d. Schusswunden,' Leipzig, 1872; 'Arch. f. exp. Path.,' Bd. i, pp. 31, 443, iii, p. 305, iv, pp. 107, 207, 409, v, p. 350, ix, p. 52, x, p. 222.

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* Buchner, 'Stzgsb. d. bayer. Akad. d. Wiss. Math.-phys. Kl.,' 1880, 7, 2.

† Cf. F. Cohn, 'Beiträge z. Biologie d. Pflanzen,' Bd. ii, Heft 2, p. 249.

‡ Koch, 'Untersuchungen über die Aetiologie der Wundinfectionskrankheiten,' Leipzig, 1878.

fever was also identical. By coupling this striking experimental result with the experiences of medicine, you will, I think, have sufficient grounds for maintaining, pending evidence to the contrary, that to each individual sharply marked infective disease there corresponds a definite equally well-marked form of bacteria; or, to express it otherwise, that each infective disease ultimately owes its characteristic peculiarities and typical course to the vital properties and life-history of the bacterium concerned in it.

This view, at any rate, harmonises perfectly with the circumstance that the infective diseases never arise *spontaneously*, *i. e.* independently, or in the absence, of a virus; not only so but it agrees above all with another remarkable fact, one of the most frequently discussed points in the history of the infective diseases—namely, their so-called *incubation.* In the great majority of infective diseases there elapses, between the infection and the appearance of the disease, a certain time, which is usually called the stage of *latency* or *incubation*, and during which the individuals often enjoy perfect health, or at least display no signs of the specific diseases. But almost more remarkable is the circumstance that the period of incubation varies in the different infective diseases, and *is wont in each one of them to last a definite number of days.* I can hardly imagine anything indeed that could more strikingly make for the parasitic theory of the infective diseases in general, and for the specific nature of the individual pathogenic bacteria in particular, than this fact, which has been repeatedly verified by the experience of centuries. For that measles should constantly make its appearance in from nine to eleven days after infection is a circumstance that cannot possibly be referred to the different quantities of poison conveyed into the body. It is all the more compatible with the idea that the contagium must first reach a certain stage of development before it can become an exciter of disease. After inoculation with the spores of anthrax, the disease arises only when the spores have become bacilli; and after partaking of flesh containing trichinæ, the characteristic signs of trichinosis, with fever and pain in the muscles, are not developed, till the original trichinæ have been transformed into intestinal trichinæ, and these have given origin to a new generation. The number of trichinæ consumed may influence the degree and severity of the entire disease, but cannot alter its typical course. Thus everything points to the existence of a *contagium vivum;* while against this view but one objection is at present raised, the justice of which we willingly admit—namely, the failure to demonstrate them in many of the infective diseases.

If we apply these general results to the infective inflammation, we should, in my opinion, formulate the principle thus—*it is bacteria that cause such an alteration in the vessel walls of certain localities that the inflammatory disturbances of the circulation result therefrom.* That the particular schizomycetes, having entered the juices of the body, should establish themselves in definite parts or organs, depends undoubtedly on the same affinity, which leads the young trichinæ born in the intestinal canal, to settle finally in the voluntary muscles, *i. e. on the fact that nowhere else do they find a suitable nutrient material ready for them.* But however much there may be to favour this assumption, you will not attach too much importance to it, for, in the first place, it is not proven, and in the second, it is an hypothesis of a very general and very tentative kind. For how this action of the schizomycetes on the vessel walls takes place has not, so far, even been guessed at. With regard to the bacteria of putrefaction and the micrococci, we thought ourselves justified in assuming that it was the chemical changes, occurring in the juices and tissues *pari passu* with the multiplication of these organisms which called forth the characteristic inflammatory alteration of the vessel walls. It is possible—there is nothing against it at any rate—that analogous changes in the fluids and tissues may be inaugurated by the specific bacteria of the infective inflammations, from which changes then the alteration in the vessels of the particular localities would result. If this is so; if *e. g.* cerebro-spinal meningitis actually arises from the settlement of particular schizomycetes in the tissues of the *pia mater*, as being the most suitable soil for their nourishment, and if the disease depends on the production of such chemical changes, through their multiplication and further development, that the vessels of the pia are altered thereby, then we are justified, it seems to me, in regarding the metastatic inflammations and abscesses in pyæmia, as well as the severe forms of traumatic inflammation, as a special variety of the *infective* class. This variety is distinguished from the other, much more markedly specific, infective inflammations by the circumstance that it owes its origin to bacteria *which appear to exist at all times in all portions of the inhabited globe.* This would supply an easy explanation of the fact that a wound may anywhere run a bad course, that an erysipelas, or even a pyæmia, may appear as an isolated or, to employ the *terminus technicus, sporadic* disease; though many lamentable experiences establish beyond all doubt the pronouncedly contagious character of these affections. For while the particular bacterial germs are indeed universally distributed, the danger of infection increases, as might be expected, when a person with an open wound is in close proximity to an individual in whom a specially prolific brood-focus of these germs has developed.

This being the mode of infection, the old definition, according to which, amongst other things, the infective diseases cannot arise at all times and in all places, must be abandoned. Yet it will not have escaped your notice that this limitation is concerned with a point of very subordinate importance, and is just as little essential as is the division of these diseases into contagious, miasmatic, and contagious-miasmatic. For we, in speaking of the infective diseases, lay the chief weight *on the parasitic nature of their cause*, or, as it is also termed, *the organised nature of the virus;* and we now know that it depends solely on the biological characters of these parasitic organisms whether the poison is conveyed into our bodies from a diseased individual, or with the inspired air, or in water, &c. Since these subordinate criteria began to be disregarded, the group of infective diseases has, during the last few years, gradually but steadily extended its boundaries; and with the infective inflammations are now classed many diseases for which a short time ago an etiology of this kind was not even thought of. To show how justifiable is this abandonment of the old traditions, let me remind you of a circumstance in your every-day experience. That an ordinary catarrh of the nose, larynx, throat—what, in short, is known in common parlance as "a cold"—is extremely infectious, the public and the physician have long been agreed; and yet such a disease, whose cause, accordingly, possesses a marked reproductive capacity, was supposed to be capable of being generated by variations of temperature, wind, rain; in short, by atmospheric influences. This change in our views is, however, chiefly to be attributed to the fact that, by a closer attention to the history of previous illnesses and to the dependence of one anatomical condition on another, we have learned to refer many inflammations, which were formerly looked on as independent, to other undoubtedly infective diseases as their cause. In the case of pleuritis and of peritonitis such a connection has long been maintained by pathological anatomists; and with regard to numerous examples of endocarditis and of meningitis there had been still earlier a disposition to take a similar view. More recently, however, Wagner,* after carefully examining the facts accumulated by him during his extensive experience, has come to the conclusion that the vast majority of all cases of nephritis are developed secondarily in consequence of some antecedent infective disease. Since then, evidence of a precisely analogous kind has been brought forward in some essays by Lücke† and Leber,‡ which will repay perusal; the former dealing with inflammations of bones and joints, the latter with deep-seated inflammations of the eye. Consider, moreover, that, owing to the progress of pathologico-anatomical research, some inflammations whose causes appeared altogether enigmatical, *e. g.* the congenital valvular diseases due to intra-uterine endocarditis, further, the so-called systemic diseases of the spinal cord, as they are termed at present, have been divested of their inflammatory character;§ and it is obvious that the number of inflammations, depending on completely unknown and, in their essence, incomprehensible causes, is decreasing more and more. We are not yet in a position, when dealing with the etiology of the inflammations, to discard the notion of a *rheuma*, *i. e.* an abnormal condition of the skin, or mucous membrane, or of the organism in general, produced by matters contained in the atmosphere; yet if I am not altogether deceived, medical science is rapidly advancing in this direction.

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* E. Wagner, 'D. A. f. klin. Med.,' xxv, p. 529.

† A. Lücke, 'D. Z. f. Chir.,' 1880, p. 300.

‡ Leber, 'Bericht d. 12 Ophthalmolog. Versammlung,' 1879.

§ Cf. Rokitansky, 'Die Defecte der Scheidewände des Herzens,' Wien, 1875; Buhl, 'Zeitschr. f. Biologie,' xvi, p. 215.

But whatever may be the causes of the inflammation, the process itself, I repeat, is always the same; and the essential character of the circulatory disturbances due to it is under all circumstances of the same kind. Hence, as already pointed out, an attempt to classify the inflammations on etiological principles exclusively, must from first to last prove unsatisfactory. One might rather be disposed to distinguish the inflammations *according to their mode of manifestation*, *i. e.* according to the symptoms to which they give rise. For the picture presented by them is highly diversified, as will seem natural enough to you from what you have already learned. I have not so much in mind the intensity of the symptoms marking the course of the entire process, although this too has been made a basis for classification. There are of course robust and feeble individuals; full-blooded, as it is called, or *sanguine*, and *phlegmatic* or more relaxed; and it is obvious that in these different constitutions the course of the disease will be correspondingly modified. You will certainly not expect that, in a debilitated feeble, old man, the heat and redness, or even the exudation and pain, will reach the same pitch, as when a strong, well-nourished person in the prime of life is attacked by a pneumonia or a facial erysipelas. Still the terms *sthenic* and *asthenic* inflammations, handed down to us by past ages, may be retained, provided they be employed to express nothing more than the degree of severity with which the symptoms of inflammation are manifested. The most characteristic example of asthenic inflammation is the so-called *hypostatic*, whereby is understood that variety which sets in in the train, and as the result, of *hypostases*. For in these cases we have to do not merely with generally debilitated individuals, but, in addition, with inflammations in organs, the circulation through which is especially enfeebled. Slight injuries are here sufficient to call forth inflammation; and when this has developed, its symptoms may be so obscure as to completely escape the notice of the patient, and to be discovered only by a careful examination on the part of the physician.

I would lay far more stress on *the modifications of the picture in its details* than on these differences in the general character of the inflammation. Yet we have already considered most of these details; as the various degrees of redness, the various elevations of temperature, the various amounts of painfulness and functional disturbance; and, in discussing the inflammatory tumor, we dwelt on the different forms in which this makes its appearance, so far as these differences are dependent on the anatomical structure of the inflamed organ. But it seems desirable to spend a little more time on the subject of the tumor; because, so different is the *habitus* assumed by it in the *same* organ, that it has been supposed to offer a suitable basis for classification. Please call to mind, first of all, that we ourselves have admitted, on *a priori* grounds, the possibility that the tumor may be altogether absent, or remain within such limits as to be the mere expression of increased fulness of the vessels. This would occur, we said, when the increase in the transudation does not exceed the functional capacity of the lymphatics of the inflamed part. Such a condition is, in fact, presented by many *superficial* inflammations of the skin, as, for example, by common erythema from exposure to the sun; and, as already indicated, in my opinion by the so-called acute exanthemata as well. That the quantity of lymph leaving the skin is increased in the latter diseases has, as you may imagine, not yet been established. But we have other evidence to show that the redness is not due to fluxion merely, but is actually dependent on a true inflammatory hyperæmia. At any rate, I can conceive no simpler explanation for the, I may say, invariable *desquamation of the skin* in scarlet fever and measles than would be afforded by assuming a somewhat intense impairment of the nutrition, the metabolism, of the skin, which itself might very readily be conditioned by an inflammatory disturbance of the circulation, but could not possibly be occasioned by a simple fluxion, even though this lasted several days. There is, moreover, the fact that the increased permeability of the cutaneous vessels during, and especially after, scarlet fever is often enough demonstrated *ad oculos* by severe *anasarca;* which proves only too clearly that the skin affection continues after the exanthem has faded and desquamation taken place. When, however, as has been observed in isolated cases, the skin becomes œdematous during the course of the fever, the inflammation is thereby approximated to that form which is usually designated *inflammation with serous exudation,* or simply, *serous inflammation.*

Meanwhile, it is well to distinguish here between two different conditions. An inflammatory exudation may, in the first place, become *serous, i. e.* resemble a simple transudation, *owing to an unusual diminution in its albuminous contents.* This state of things is found in individuals whose blood-serum has become abnormally thin through the loss of large quantities of albumen, *e. g.* in nephritis. In such individuals inflammation is frequently and very readily excited, apparently because the vessels, being already poorly nourished by the watery blood, are more powerfully affected by comparatively slight injurious influences. The amount of the exudation in such patients is also at all times very considerable, while the concentration, on the contrary, is, as has been said, proportionately slight. That the dilution of the blood is actually responsible for the altered constitution of the exudation may be readily proved by experiment. If you collect the lymph from the inflamed paw of a dog in the way I formerly described, and then create a hydræmic plethora by injecting large quantities of 0·6 per cent. solution of common salt into the v. jugularis, the lymph at once begins to flow more abundantly, but its solid contents decrease in proportion*—a precise parallel, as you see, to the inflammations occurring in persons suffering from nephritis. In the second place, an inflammatory exudation acquires a certain resemblance to a serous transudation, *when the number of its formed constituents, or blood-corpuscles, is very small.* In what circumstances this will be the case you are already well aware. You know that in the early stages of the inflammatory exudation, before the emigration of corpuscles is properly set going, a clear fluid transudes through the vessels; and you know, on the other hand, that where the injurious action is the vessels has been slight, the alteration in the transudation may be entirely confined to an increase in the fluid without any augmentation in the extravasation of corpuscular elements setting in at any time. True croupous pneumonia commences with so-called *engorgement, i.e.* hyperæmia with œdema; out of every wound there trickles at first a clear fluid, in which but few pus- and blood-corpuscles are contained. The contents of a vesicle raised by vesication consists solely of a serous fluid containing some isolated corpuscles suspended in it; and after a slight burn or freezing, moderate œdema is the only result. This is all very simple, and I should hardly have thought it necessary to touch on these circumstances once more, did I not at the same time desire to direct your attention to the relative frequency of serous inflammations in pathology. It is true that, except in hydræmic individuals, genuine inflammations, in which the exudation consists *solely* of a serous fluid, occur but rarely as independent prolonged diseases; yet one occasionally comes across a pleuritis with serous exudation; not only so, but many œdemas of the pia mater, many hydroceles, many a case of hydrocephalus, might be correctly placed under this head. Still commoner than these, certainly, is the local combination of serous exudation with the severer forms of inflammation. When in a lung of which the lower lobe and lower portion of the upper lobe are hepatised the alveoli of the air-containing lobuli are found bathed in fluid, this is nothing more or less than an *inflammatory œdema.* Moreover the so-called *œdema glottidis* or *œdema circa glottidem,*which proves so dangerous to individuals who, for example, suffer from deep ulceration of the larynx, is of inflammatory origin; and when in an empyema, *i.e.* a purulent pleuritic exudation, *the subcutaneous cellular tissue of the affected half of the thorax becomes, as very often happens, œdematous,* this is neither a collateral œdema, nor is it, as was formerly supposed, an œdema due to mechanical hyperæmia. For the notion of a so-called collateral œdema is, as you know, unscientific; and how could the efflux from the veins of the wall of the thorax be obstructed by a purulent pleuritis, since the anastomoses and efferents permitting the escape of venous blood are really innumerable? The œdema is simply *inflammatory;* it is, so to speak, the last wave of the process whose centre lies in the severely diseased pleura.

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* O. Lassar, 'Virch. A.,' lxix, p. 516.

I need hardly add that the presence of some blood- and pus-corpuscles in a serous exudation is not excluded. Even when a few delicate and soft flakes of fibrin are found floating in it, it does not therefore cease to be serous. For what is so often true holds good here also: *a potiori fit denominatio.* We do not speak of a *fibrinous exudation*, or of a *fibrinous* or *croupous inflammation*, till a copious separation of albumen by spontaneous coagulation has taken place. The inflamed surfaces are then covered by thick layers of soft fibrin, which are sometimes smooth and sometimes wavy or shaggy; bulky flakes of fibrin float in the exudation; and if channels or cavities exist in the inflamed organ, these are filled and more or less plugged by fibrinous casts. Typical examples are met with in the serous membranes and also in the lungs. On examining these fibrinous membranes microscopically we find pus-corpuscles to a variable amount enclosed in a material which is partly fibrillar and partly granular. The corpuscles are sometimes almost altogether wanting, and at other times so numerous that the fibrinous layer appears to consist of nothing but dense accumulations of these cells. Red blood-corpuscles are also frequently included in the pseudo-membrane, but always in small quantity; simply because the greater part of them remain in the tissue surrounding the vessels out of which they have extravasated. As to the *amount of fluid*, which, with the fibrin, constitutes the exudation in fibrinous inflammations, no general rules can be laid down. In a fibrinous pericarditis accompanied during life by the most typical friction-sound, there is sometimes found, besides the shaggy coating of the internal surface of the pericardium, only a few grams of watery fluid, while at other times the pericardial cavity is so distended that the lungs are displaced to the back part of the thorax: between these two extremes there are all possible gradations. Now what does the presence of fibrin in an exudation signify? The fact that spontaneous coagulation may ensue in inflammatory transudations will not, I think, appear specially remarkable, when you consider that the fluid portion is derived from the blood-plasma, and that colourless blood-corpuscles are anything but deficient in the exudations. Or is one to assume gratuitously that the fibrinogen does not participate in the transudation? On the contrary we should, I believe, *a priori* regard every inflammatory exudation as *coagulable;* so that a separation of fibrin may be expected to occur as soon as a certain quantity of colourless blood-corpuscles have become mingled with it. Thus you found it perfectly natural that a fibrinous pseudo-membrane should be developed on the surface of the exposed mesentery, and the richness in pus-corpuscles was just as little surprising to you there as in the case of the white thrombus. Under these circumstances, it would be at bottom much more remarkable, were *no* separation of fibrin to occur in an exudation. Yet you will please remember, in this connection, that the presence of numbers of colourless blood-corpuscles is not alone sufficient for the formation of fibrin, but that their *disintegration,* their *death,* is necessary; since only by their destruction is the fibrin-ferment set free. The non-occurrence of coagulation in an inflammatory product may, accordingly, depend either on a deficiency of blood-corpuscles, or on the circumstance that somehow or other the vitality of the corpuscles is maintained and their destruction prevented. The first factor, the poverty in colourless corpuscles, obtains in inflammations with a serous exudation; and it also sufficiently explains how it is that the absence, or slight amount, of the fibrinous deposit observed in such exudation should also be found in those localities where there are no anatomical arrangements for maintaining large quantities of colourless blood-corpuscles intact after they have left the vessels, *e. g.* the serous membranes. For it is owing to the want of such arrangements that the inflammations of these membranes become so typically fibrinous as soon as a considerable number of blood-corpuscles have appeared in the exudation. But how as regards inflammations of the mucous membranes, where the number of pus-corpuscles present in the exudation may be enormous, and yet no coagulation occurs under ordinary circumstances? Now as to these inflammations, it can be proved to demonstration that fibrin fails to be deposited only *because the extravasated blood-corpuscles are kept from perishing.* Their preservation is due, as has been shown by

Weigert,* to the presence of the *mucous epithelium;* when the epithelial cells perish or are completely and lastingly destroyed, the exudation takes the form of a fibrinous pseudomembrane, such as may be observed in artificial or naturally occurring *croupous* inflammations of the membrana mucosa. Similarly when in violent, but not purulent, inflammations of parenchymatous organs or other tissue, *e. g.* in the so-called interstitial inflammations of the liver, kidneys, muscles, &c., no coagulation occurs, this depends essentially on the fact that the white blood-corpuscles which have collected in the meshes of the tissues can readily maintain their vitality there.

But certain inflammations of other organs, of the serous membranes for example, do not at all admit of a similar explanation. In these the exudation is *purulent,* pus-corpuscles being present to an unlimited extent, and but few or no flakes of fibrin. The inflammatory product here consists of a creamy, mostly somewhat consistent, yellowish or (when, as often happens, red blood-corpuscles are mingled with it) reddish-yellow, opaque, generally odourless fluid, in which only a few delicate or more bulky flakes of fibrin float, or these may be altogether absent. When fresh pus is examined microscopically, nothing is found in it, as a rule, but pus-corpuscles and a few red cells, suspended in a colourless fluid. Pus occupying a circumscribed portion of the tissues is called an *abscess*; when more diffused it is known as *purulent infiltration;* when situated in a natural cavity we speak of it as a *purulent effusion.* How little preventive influence is exerted by the anatomical structure of the inflamed organ on the deposition of fibrin in purulent inflammatory affections is most clearly demonstrated by the fact that the exudation of pus is in very many cases preceded by an exquisitely fibrinous inflammation. In pleuritis the physician very commonly finds the unmistakable signs of a fibrinous exudation followed by those of an empyema, and the flakes discovered floating in a purulent effusion of the pericardium or peritoneum are usually nothing but the remains of a copious deposition of fibrin. This circumstance is well calculated to place the significance of the purulent exudations in a proper light. For it shows unmistakably that the purulent inflammation is a *severer* form than the fibrinous, which latter becomes purulent only when it does not go on to absorption. This rule is indeed true of all purulent inflammations, whether they have been developed from an antecedent fibrinous form, or have from the first, or at least very early, assumed the characters of the specifically purulent one. *The inflammation whose product is purulent is always severe*, although its import for the organism as a whole may be trifling, owing to the small size of the inflamed area.

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* Weigert 'Virch. A.,' lxx, p. 461; cf. Section ii, Chap 1, Diphtheria.

Yet it would be fatal to regard inflammation with purulent exudation, or, more briefly, *suppuration*, as a mere *quantitative augmentation* of a process remaining in other respects identical. We shall presently make the acquaintance of another variety—the hæmorrhagic exudation—to which an especially severe and malignant character may with still more justice be attributed, and which, nevertheless, has nothing in common with suppuration. The assumption of the purulent form by the inflammatory product also involves an intimate *qualitative* change in the entire exudation. The nature of this change we are still far from able to define completely. Its most remarkable feature at least is that of *preventing the formation of fibrin*. The colourless corpuscles are not transformed into fibrin, and instead of losing their nuclei, there are seen almost universally in the pus-cells several separate nuclei, or nuclei of trilobate form—a condition which was long supposed to be indicative of the progress of cell-multiplication, but which, in view of the important extension of our knowledge with regard to the division of nuclei, must now be judged of more cautiously, and may perhaps be regarded as a process of disintegration. But not merely is the formation of fibrin prevented *in statu nascenti*, if I may use the expression; what has already been formed and separated is dissolved through the suppuration, or the flakes are at least softened and loosened. Indeed, if the suppuration occurs in a tissue, even the solid constituents of the latter may undergo liquefaction. The chemical agent—for such must be its nature—engaged here has so far completely escaped recognition. One might incline to seek it in the carbonic acid which, as was determined by Ewald,* is present in suppurating tissues under very considerable tension; yet while it is true that this gas may retard coagulation, it is incapable of preventing it, nor can it by any possibility bring about the solution of fibrin already deposited, much less of fully developed tissues. Further, since it has been shown in Ludwig's laboratory[*] that peptone when injected into the blood keeps it from clotting, the idea naturally suggested itself that the peptone, whose presence in pus has of late been repeatedly determined, may possibly play a part in hindering coagulation. Yet, to say nothing of other objections, this supposition is negatived by the fact that the extract obtained from a piece of lung affected with croupous pneumonia, by treating it with water, gives a marked peptone-reaction.[‡] On the other hand, we are much better acquainted with the *conditions* under which an exudation becomes purulent. For we know that the agent causing suppuration, or, as it may be briefly termed with Weigert,[§] the *pus-poison*, is always introduced into the human body from without, its form in the vast majority of cases being that of an *organised, infective virus*. To the doctrine that the capacity for exciting suppuration inheres *exclusively* in an organised material of infection I am unwilling to subscribe at present, for a purulent inflammation may be produced with absolute certainty by injecting turpentine, petroleum, or more especially croton-oil into the subcutaneous areolar tissue of a dog, and I cannot admit that the entrance of lowly organisms into the body has so far been proved to take place in all these cases. According to Riedel[‖] the same result attends the injection of clean quicksilver into the knee-joint in rabbits. True, with regard to the purulent inflammations observed in human subjects, in which such agencies as those just enumerated may almost always be excluded, we are already justified in laying it down as a rule, having practically no exception, that they owe their origin to organised infective materials. But here if anywhere is the necessity for sharply distinguishing between the various infective organisms apparent. For every purulent inflammation except those just mentioned is infective, but it is not every infective inflammation that is purulent. Croupous pneumonia, the pericarditis of rheumatic fever, epidemic angina, and many other maladies are truly infective in their nature, and yet no purulent exudation occurs in them; or should it set in, does so only as the result of some complication or sequela. The bacteria which produce the pus-poison, or, if you prefer it, themselves act as such, are only certain definite kinds. We have mostly to do here with organisms having the form of micrococci, and this is more especially the case in the entire group of suppurative processes to which the term "sepsis" in its widest sense is at present applied. Under this head I place suppuration of wounds, phlegmonous erysipelas, suppuration in joints and glandular organs, metastatic and secondary suppurative inflammations of serous membranes, and, lastly, pyæmic suppuration with puriform softening of thrombi, &c. The organisms found in gonorrhœa and in purulent conjunctivitis also appear to have the micrococcus form.[*] Yet you will not conclude from this that micrococci and pus-poison are identical. For, on the one hand, there are pathogenic micrococci which, like that of simple erysipelas, are in nowise provocative of suppuration; while, on the other hand, organisms in every respect distinct from micrococci are present in many typical suppurations. Thus leptothrix-threads[†] are sometimes met with; further, the so-called *ray-fungus* or *actinomyces*,[‡] a fungus bearing conidia and evidently approaching closely the hyphomycetæ, which was first recognised in cattle and has more recently been repeatedly observed in man; while even varieties of a genuine and undoubted mould, the *aspergillus glaucus*, have been found.[§] But whatever the form of the organisms involved, it is certain, I again repeat, that in their absence a true pathological suppuration occurs, if at all, only in the most exceptional cases. You will, at any rate, do well to hold in practice to this principle, which has almost never disappointed me since I adopted it. When dealing with a purulent peritonitis, try to discover from which of the organs bordering on the peritoneum bacteria could have penetrated its cavity. In a suppurating phlegmonous erysipelas seek chiefly to discover the wound or abrasion of the skin which has permitted the entrance of micrococci into the cellular tissue. When you meet with genuine suppuration in a cystic tumour of the ovary, you may assume with almost mathematical certainty that if there was no other antecedent interference, a puncture at least had been made; and similarly the trochar but too often causes an ordinary pleuritis to change into the purulent form. In the eye, also, organisms are the sole cause of the hypopyon and keratitis after slight injury of the cornea; and to them it is due that a purulent panophthalmitis follows the passage of a thread through the eyeball. Hence the former is most readily set up when disease of the lachrymal sac already exists.* H. Grenzmer, while experimenting in our Institute, succeeded in passing threads through the globe without severe consequences of any kind, and even secured the healing of the eye while the threads remained in position. This result was attained by perfect disinfection of the threads themselves, careful cleansing of the sac of the conjunctiva prior to operation, and absolute protection by antiseptic bandaging against the entrance of schizomycetes into the interior of the eyeball at the point of puncture.

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* Ewald, 'A. f. Anat. u. Physiol.,' 1873, p. 663, 1876, p. 422.

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[*] Schmidt-Mülheim, 'A. f. Physiol.,' 1880, p. 33.

[†] Hofmeister, 'Zeitschr. f. physiol. Chemie,' iv, p. 268.

[‡] Sotnitschewsky, ibid., iv, p. 217.

[§] C. Weigert, 'Virch. A.,' lxxix, p. 87; cf. also this writer's thoughtful article "Entzündung" in Eulenburg's 'Realencyklop.'

[‖] Riedel, 'D. Zeitschr. f. Chir.,' xii, p. 447.

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[*] Neisser, 'Med. Ctbl.,' 1879, p. 497.

[†] Weigert, 'Virch. A.,' lxxxiv, p. 314.

[‡] Bollinger, 'Med. Ctbl.,' 1877, p. 481; Israel, 'Virch. A.,' lxxiv, p. 15; ibid., lxxviii, p. 421; Rosenbach, 'Ctbl. f. Chir.,' 1880, No. 15; Weigert, 'Virch. A.,' lxxxiv, p. 303. Two cases, observed by Ponfick, have not yet been thoroughly described, but have become known through lectures, which P— has delivered in some of the larger towns of Germany, Berlin, Bremen, Breslau, Dantzig, &c.; cf. 'Bresl. ärztl. Zeitschr.,' 1880, No. 12.

[§] Leber, 'A. f. Ophthalmol.,' xxv, Abth. 2, p. 285.

We have to notice lastly the inflammations with a bloody, *hæmorrhagic*, exudation, or the hæmorrhagic inflammations, *i. e.* those forms in which the exudation contains so many red corpuscles as to acquire the colour of blood. You are, however, already acquainted with the conditions in which an exudation becomes hæmorrhagic. This occurs, as you will remember, when the retardation of the blood-stream in the inflamed area is so considerable as almost to give rise to stagnation in some of the capillaries. But this again implies an especially severe alteration of the capillary walls, which itself may result either from the exceptional intensity of the noxa exciting inflammation, or from unusually feeble powers of resistance on the part of vessels. To which of the two factors the condition should be referred, or whether a combination of both is present, must of course be decided by an examination of each individual case. Inflammations terminating in gangrene often have a more or less hæmorrhagic character. An exquisitely hæmorrhagic pericarditis has been observed as an epidemic amongst soldiers and sailors who had lived long under very unfavorable hygienic conditions. Severe inflammations of so-called *constitutional* origin, as the pleuritis, pericarditis, and peritonitis which are associated with the eruption of tubercles or cancer-nodules on the affected membranes, are specially predisposed to become hæmorrhagic; probably because the vessels of the membranes in question are often involved in the tuberculous or cancerous process, and also because whatever new vessels may be developed under such circumstances are from the first provided with imperfectly formed walls.

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* Cf. Leber, 'Med. Ctbl.,' 1873, No. 9.

These are the principal forms assumed by the inflammatory exudation. They have often been made the basis of a classification of inflammations; yet I need not point out that the types which have been described do not always appear in this pure unmixed manner. Have I not attempted to explain how the boundary between serous and fibrinous exudations must from the nature of the case be ill-defined, and how, on the other hand, a fibrinous exudation may be transformed into a purulent one under the influence of the pus-poison? Hence it is not only conceivable but necessary that, besides the purely serous, fibrinous, and purulent exudations, *fibrino-serous* and *fibrino-purulent* combinations should exist. But even allowing for this, you will often enough meet with inflammations which do not correspond to the types as delineated, but display a more or less different habitus. Indeed the examples last cited, the hæmorrhagic pleuritis and peritonitis of tubercle or cancer, are strikingly distinguished from simple inflammations by the presence of tuberculous or cancerous nodules. Yet these have in themselves no direct connection with the inflammation and are at most co-effects of the cause producing it. At other times, also, it is usually some complication that obscures, or even effaces, the typical picture of inflammation. To this category belongs the more or less deep *necrosis* occurring in diphtheritic inflammations, to which reference has already been made, and which will afterwards be discussed more thoroughly. Here too must be placed the various *phenomena of degeneration and repair* which, as we shall see presently, very commonly arise in the train of inflammation, and under the influence of its exciting cause. In the last place, the physiological peculiarities of an organ or tissue may help to modify very essentially the constitution of the exudation. Thus many elements combine to give the simple inflammations of the *mucous membranes* a peculiar stamp. Inflammations of these membranes may be accompanied by a purulent exudation; not only so, but the *blenorrhœas* of the urethra, conjunctiva, vagina, and occasionally of the bronchi or large intestine, present some of the best opportunities for observing typical and profuse suppurations. On the other hand, fibrinous inflammations of the mucous membranes occur, as already mentioned, only when the epithelium has been totally destroyed or has undergone necrosis. Hence when no coagulum, but only fluid, is poured out on to the surface of an inflamed mucous membrane, we are not entitled to look on the process as being for this reason especially mild. That commonest form of inflammations of mucous membranes, *catarrh*, is an example in point. Of catarrhal, as contrasted with croupous or diphtheritic, inflammations, it is characteristic that the epithelium is not lost, but living and active. True, that it should behave quite normally is not to be expected, the less so as it is very common for some of the epithelial cells, or even layers, to be involved in the damage done by the exciter of inflammation. The regular appearance of epithelium, and of matters derived from it, in the catarrhal inflammatory product is thus without difficulty explainable. But few intact epithelial cells will be found in the exudation as a rule; while as regards epithelial derivatives, the knowledge we at present possess of the life-history of the epithelia is far from enabling us to explain with certainty the origin of each particular form, and from allowing us in particular to judge how many and which of them are due to regenerative processes. That cubical or polygonal epithelial cells will readily assume a globular form, on being set free from their membranous connection, is easily understood; and from Volkmann and Steudener[*] we have learned that those remarkable structures, formerly regarded as proving an endogenous formation of pus-corpuscles within the elements of the epithelium, namely, large cells of clearly epithelial character, including within them one, or it may be several, pus-corpuscles, are really formed by the immigration or *invagination* of the latter into the epithelial elements. But *ciliated amœboid cells* have also frequently been seen in the inflammatory products of mucous membranes the epithelium of which is ciliated,[†] and what relation the so-called *mucus-corpuscles* hold to the epithelial cells is still very questionable. Yet though the whole subject still requires adequate investigation, it has at least been established beyond all doubt that the anatomical picture presented by an inflamed mucous membrane corresponds essentially to the type of inflammations in general. Neither the overloaded vessels nor the immense quantities of pus-corpuscles are wanting; the latter lying in closest proximity to the veins and capillaries, as well as distributed throughout the meshes of the mucous tissue and in and between the epithelial cells; the red corpuscles are also more or less numerously represented. In the epithelial cells of the mucous glands, as well as in the statified mucous epithelium itself, the well-known *hyaline droplets* are often seen when the catarrh is recent; they appear to be connected with the *production of mucin.* For, however its composition may vary in other respects, the secretion of every mucous membrane contains mucin; hence we have a further peculiarity of the catarrhal inflammatory product, no less characteristic than the occurrence of epithelial elements, namely the constant presence of this substance. The exudation is *mucous* or perhaps *muco-purulent.*

But however ill or well defined these various forms of exudation may be, their most important feature in any case is that they all may be traced back, as has just been attempted, to one inflammatory process. Thus they nowise represent differences in the process itself, but merely certain modifications in the form of the inflammatory tumor. The process is

[*] Volkmann und Steudener, 'Med. Ctbl.,' 1868, p. 257; Steudener, M. Schultze's 'A. f. mik. Anat.,' iv, p. 188.

[†] E. Neumann, 'Med. Ctbl.,' 1876, p. 417.

always in its essence one and the same. To recapitulate once more the main features of inflammation: it invariably commences with a dilatation of the vessels, which sets in either rapidly, or slowly and gradually, according to the cause of inflammation. In the former case the vascular dilatation depends at first on a diminution of resistance due to relaxation of the tonus, and like every true congestion, is accompanied by an acceleration of the blood-stream. Thus it is, for example, in inflammation after scalding or the exposure of deep-seated parts to the atmosphere, and thus it will certainly be where the sensory nerves of the affected area are strongly irritated by the cause of inflammation. Should, however, the exciter of inflammation not produce an immediate lowering or complete relaxation of tonus, the dilatation of the vessels is slowly developed, in dependence on the gradually increasing molecular change in the vessel walls. Yet in the other class of cases also the hyperæmia of congestion is followed by this same dilatation, an event which is announced by a further increase of the calibre of the vessels, but more particularly by the gradual conversion of the acceleration into a slowing of the blood-stream. For the distinguishing character of true inflammation as compared with fluxion is the *diminution* in the velocity of the flow through the dilated vessels, due to the increase of the resistance arising out of the molecular alteration in the vessel walls. When this point has been reached, and *pari passu* with the slowing of the stream, the pavementing of the veins with colourless blood-cells and the accumulation of corpuscles in the capillaries have taken place, the *first stage* of inflammation is completed. At least it appears to me that if the series of events under consideration are to be classified according to their order of sequence, the most natural arrangement will be to make the first period terminate with the establishment of these characteristic phenomena in the interior of the vascular lumen. Hence, among the cardinal symptoms, only the *rubor* and *calor* will distinguish the first stage of inflammation; while the *dolor* and *functio læsa* are wont to be present, if at all, only in their earliest beginnings. The *tumor* will at any rate be absent, or will not exceed that of simple fluxion. The development of the inflammatory *tumor* is characteristic of the *second stage*;

yet it must be admitted that this stage cannot be sharply distinguished from the first, since the transudation undoubtedly is gradually increased as soon as the stream becomes slower. The entire process, which up to this point displays everywhere the same *habitus*, henceforth assumes the most different characters in accordance with the various anatomical regions which are the seat of the inflammation, and the various modifications which the exudation undergoes. You will gladly dispense with detailed proofs of this statement, as we have some time since and also recently devoted ourselves with such thoroughness to the discussion of the constitution of the tumour. Nor need I again remind you with respect to the sequence of events characteristic of inflammation that inflamed parts have a more intense red colour in the early stages, while the more abundant the exudation and the longer it lasts, the greater is the tendency to assume a gray or grayish-yellow hue—provided the inflammation in question is not hæmorrhagic. But whether the exudation be serous or fibrinous or purulent, whether it be poured out into a cavity or into the interstices and meshes of an organ, it may be said that when it has reached its full development as regards distribution and amount, the *second stage* of inflammation is complete. In this stage the entire process has attained its highest pitch. Having followed it so far, the question—what is its subsequent history, naturally suggests itself; and we shall now attempt to answer it, the more willingly as we may fairly anticipate that valuable information as to the significance of inflammations for the organism will at the same time be afforded us.

And first of all we have to notice that the course of an inflammation may during its development be any moment cut short by the death of the individual—a much rarer occurrence, it is true, in the first than in the second stage. Indeed there is hardly a morbid process which more often terminates in death. But on inquiring in what manner life is destroyed, we find that the danger arises, not so much from the circulatory disturbance itself as from the secondary changes called forth by it. In this respect nothing is more important than the *pyrexia*, which so often accompanies inflammation of any degree of violence. In many infective inflammations this sets in even before the circulatory disturbance has reached any considerable degree of severity, but is in others developed in direct dependence on the inflammation and its products. With the explanation of pyrexia, its origin, and its significance for the organism, we shall have to deal in treating of the pathology of animal heat. If the fever accompanying inflammation does not lead to the fatal termination, it is mostly definite derangements of function in the affected organs that bring about this result; but for these, it is evident, no general rules can be laid down. The very unequal vital importance of the various organs renders it, moreover, comprehensible that the same process may in some cases be without importance *quoad vitam*, and in others prove fatal, even though in the latter it should be less violent and extensive. An inflammation involving the muscles of the arm or leg results at most in a temporary impairment of the function of the extremity, while one attacking the diaphragm, the intercostal muscles, and more especially the heart, may prove dangerous to life itself. Similarly a minute circumscribed inflammation of the medulla oblongata is a very grave affection, while the whole leg may become inflamed without directly threatening a fatal result. A peritonitis is more dangerous than a pleuritis of much greater severity; because a reflex proceeding from the peritoneum may cause stoppage of the heart's action—an effect which, so far as we know, cannot be produced in the case of the pleura. Extensive pneumonia, by which a very large portion of the lung is rendered useless for respiration, is always serious. The constitution and age of the patient also play a part not difficult to understand. A catarrhal inflammation of the intestine kills a little child, while an adult easily resists the digestive disturbance occasioned by it. The same bronchitis which proves fatal to an old man, a child, or an individual suffering from heart disease is a very trifling affection in a person in robust health. Indeed, even simple mechanical conditions may have their importance; for an exudative laryngitis or tracheitis can cause suffocation in a child, a danger which is not much to be feared in an adult with his more spacious larynx.

Next to this, the most unfavorable of all the possible terminations of inflammation, may be placed that of *local death*, *necrosis.* The local combination of necrosis and inflammation is, *per se*, one of the most frequent occurrences in pathology, yet two different *modi* are to be distinguished here. With local necrosis, as constituting one of the commonest causes of inflammation, we have ourselves become acquainted, and we shall have to speak more particularly of this relationship when discussing the subject of gangrene. We shall then find in so-called diphtheritic inflammation a process whose central point is necrosis, and whose entire course is determined more by the necrosis than by the inflammation. On the other hand, there are not a few cases where a true, indubitable, primary inflammation leads to the death of the tissues, and to these we shall now turn our attention. The possibility of such a termination will not surprise you, if you call to mind the considerations with which we introduced the subject of inflammation (p. 247). We were then able to state that inflammation is called forth by those *noxæ* precisely which, if their action be either prolonged or intensified, cause the death of the part concerned. We saw that at the seat of application of a caustic death is the result, and that as we proceed away from this point we find in the surrounding tissues an inflammation of gradually decreasing intensity. A part when exposed for a short time to cold of $-6°$ to $-8°$ becomes inflamed ; when its temperature is reduced to $-16°$ to $-18°$ it dies, and death also occurs when the slighter degree of cold has been maintained for a longer time. In precisely the same way we see inflammation of an ear after ischæmia of twelve hours' duration, but death after this condition has lasted for from twenty-four to thirty-six hours ; and similarly a protruded loop of intestine inflames first of all and then, if left longer exposed in an unprotected state, dies. These facts make it comprehensible, in the first place, that certain severe inflammations should terminate in gangrene when the noxa exciting inflammation *continues operative*. But that, in the next place, a very violent inflammation should sometimes lead to mortification of the affected part, even in the absence of this aggravating circumstance, admits, I think, of explanation. You will constantly bear in mind that the vessel walls are living organs whose metabolism is probably very active, and whose life, like that of all portions of the animal body, is intimately dependent on the constant maintenance of a certain regularity of the circulation. Now, if the vessels which have been affected to a high degree by an intense noxa were, the moment this noxa ceases to operate, again supplied by the normal blood-stream, it could not reasonably be doubted that their normal constitution would after a longer or shorter period be restored. In reality, however, the blood-stream is under these circumstances thoroughly abnormal, in particular markedly retarded; and what could be more natural than that the vitality of the capillaries in which the flow has been for some time greatly reduced, through whose walls moreover a transudation of entirely altered character percolates, should become feebler and feebler and finally be extinguished? Stagnation then becomes *stasis, i. e. complete stand-still of the blood with coagulation;* and whenever a somewhat extensive stasis has occurred in a part, necrosis is the inevitable result. You now understand how it happens that inflammations which terminate in gangrene so readily acquire a hæmorrhagic character. Rather the connection is the reverse of this; *inflammations of such severity as to be attended by hæmorrhagic exudation are specially predisposed to end in necrosis.* Thus when in a rabbit's ear, from which the blood-supply has been cut off for from sixteen to twenty hours, you see numerous profuse hæmorrhages, you may with absolute certainty count on the speedy appearance of more or less extensive mummification as a sequel to the large primary typically inflammatory swelling. The variable dimensions of these necroses, together with the circumstance that for their production in some animals an ischæmia of sixteen hours suffices, while in others an ischæmia of twenty-four hours is required, is very naturally explainable from the unequal powers of resistance in different individuals. This is a factor the importance of which is apparent in human pathology also; for it is owing to the feeble powers of resistance possessed by the vessels in certain constitutional states that inflammations so readily assume a gangrenous character; as *e. g.* in *diabetic* or *hydræmic* individuals and persons otherwise debilitated; hence more particularly in the aged. In like manner very slight injuries, which in healthy persons would hardly be followed by an inflammation even of moderate intensity, are capable of producing extensive and deep necrosis in parts where hypostatic congestion exists—a sequence examples of which are but too often presented in the bedsores of typhoid patients, &c.

Contrasting with these unfavorable terminations of inflammation are the favorable ones, among which by far the most desirable is complete recovery, *restitutio in integrum.* Let us pass over for a time the repair of tissues which may have been damaged or altogether destroyed, and confine ourselves just now to that most essential element in inflammation, the circulatory disturbance itself. It need hardly be stated expressly that the circulation will be more easily restored, the less advanced the inflammation; in the first stage success is the rule, in the second it is also very frequent. Restoration is of course impossible till the inflammatory process has been checked; and to this end the cause of inflammation must first be got rid of. An exposed part must be replaced under its natural coverings; caustics, foreign bodies, dead particles must be removed; a stop must be put to the progress of putrefaction. This object is already achieved before the development of inflammation in those cases which are the result of transitory actions, *e. g.* scalding. But it is necessary to remove not merely the cause but the effect of inflammation, the alteration in the vessel walls. Here, however, the remedy is *eo ipso* presented, for it is nothing else than the *circulating blood.* It is this that maintains the composition and function of the vessels normal; an office performed for the endothelium, and probably also for the non-vascular intima, by the blood flowing through the vessel, and for the remaining coats, in the case of the larger vessels, by the blood of the vasa vasorum. Whenever, owing to the action of some injurious agency, or in consequence of deprival of its nutrient blood, the vessel wall has undergone alteration, the circulating normal blood is the simplest, most natural, and, in any case, most effectual means of restoring it to its original condition. This will be the unfailing result except where the injury to the walls has been too severe and there is presented that *circulus vitiosus* with whose pernicious effects we have just become acquainted. Should, however, the *physiological* influence of the circulation get the upper hand, the vessel walls gradually regain their normal characters, and the flow through them is restored. Moreover, the chief function of the physician is simply to maintain as far as possible the circulation; the restoration of the vessel walls, if recovery is still possible, will then take place. And from these considerations it furthermore becomes apparent why inflammations are wont to be more fatal, and to have a specially tedious course, in persons, the constitution of whose blood is defective, or in whose circulatory apparatus some derangement or other exists. The more physiological and regular the constitution and circulation of the blood in any individual, the more easily and certainly, *cæteris paribus*, does the restoration of the vessels take place.

Now when, as restoration progresses, the vessels reassume their normal calibre, and the blood-stream its normal velocity; when the pavementing and accumulation of blood-corpuscles as well as the abnormal transudation ceases, an inflammation which has not substantially passed the first stage is thereupon at an end, and the re-establishment of the original conditions existing previously to the inflammation is complete. When, on the other hand, it has gone as far as the formation of a *tumor*, the exudation must disappear before an inflamed part can regain its normal characters. As far as the fluid portion of the inflammatory transudation is concerned this is readily effected; it is simply sucked up, *absorbed* —by far the greater part, apparently, by the lymphatics. Hence it is that an inflammatory œdema or serous exudation is wont to rapidly disappear after the integrity of the vessels is restored and a stop put to renewed transudation. But the corpuscular elements and the fibrin, if present, may also completely disappear, provided they do not exceed a moderate amount. The colourless blood-corpuscles, equally with the fluid, are free to enter the lymphatics; into these they migrate, are *dispersed*—as with a correct instinct it has for ages been popularly called—in the lymphatic channels.*

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* Cohnheim, 'Virch. A.,' xl, p. 1; Hering, 'Wien. akad. Stzb.,' Bd. lvi, Abth. 2, Novbr., 1867; A. Heller, 'Untersuchungen über d. feineren Vorgänge b. d. Entzündung,' Erlangen, 1869; R. Thoma, 'Die Ueberwanderung farbl. Blutkörperchen v. d. Blut- in das Lymphgefäss-system.,' Heidelberg, 1873.

The few red corpuscles gradually lose their pigment, and slowly disintegrate, and of the fibrin even no trace remains; this substance being, it would seem, first transformed into a fatty emulsion and then, like the fluid and white corpuscles, taken up by the lymphatics.

Accordingly, when inflammation terminates in this way perfect restoration is accomplished without any loss of material by the organism, in so far at least as such has not been occasioned by pyrexia or some accidental circumstance. The realisation of this termination is materially interfered with when the exudation has become very bulky; as *e. g.* in a large pleuritic exudation, an extensive pneumonia, or a phlegmonous erysipelas. It is evident that the recovery of the vessel walls must in these cases also precede the removal of the products of inflammation, if the removal is to be really final. Yet a very bulky exudation is certainly not conducive, but rather unfavorable, to the restoration of the vessel walls, because of the impediment it offers to the circulation. And even after the recovery of the vessels, the resorption of an exudation which may be measured by the litre is not of course so simple a matter, or so rapidly effected, as where it amounts to a few grams. For though the lymph-stream is, as we formerly determined, more active in inflammation than under normal conditions, and the absorbent power of the lymphatics is then undoubtedly increased, there continues to be a very severe strain on the capacity of the latter. This is especially the case in individuals who have just passed through a severe inflammation, resulting in a considerable reduction in the energy of the blood and lymph circulation if the lymphatics have then to set about absorbing several hundred cubic centimetres of exudation, in a short space of time. Resorption will certainly take place very slowly, so that it is always very desirable, if opportunity offers, to expedite the process and help forward complete restoration. As long as the pulmonary alveoli are still filled with exudation they can take no part in the exchange of gases, even though the vessel walls have already recovered and the inflammation is therefore at an end. A joint will continue useless as long as its cavity is filled with fluid, although the abnormal transudation has ceased to be secreted by the synovial membrane.

In such cases, where resorption proves inadequate or unpleasantly tedious, the recovery of the patient is essentially furthered when a portion, or even the whole, of the exudation is removed externally. When mucous membranes are inflamed the removal is effected spontaneously. In cavities or passages which communicate with the exterior of the body, like the bronchi, pulmonary alveoli, and urinary passages free escape is also provided for. It is true that before the exudation can be removed spontaneously its solid parts must undergo liquefaction. This, however, is the rule; and I have already pointed out that unresorbed cells as well as the deposited fibrin invariably sooner or later undergo *fatty metamorphosis*. As the result of this transformation, into the history of which we cannot at present enter, the inflammatory products gradually assume a markedly yellowish colouration; so much so indeed that in pneumonia, for example, we speak of a stage of *yellow hepatisation*. Still more deserving of notice is the formation of an emulsion-like liquid which, in so far as it is not absorbed, may flow away. Thus a pulmonary infiltration, having undergone liquefaction, is in greater part expectorated, and there remains to be absorbed only that portion of the inflammatory product which is lodged in the alveolar septa. Similarly in inflammations of the mucous membrane only the infiltration of the tissues is removed by absorption. In other parts, with which there is no external communication, the skill of the surgeon comes to the aid of nature by artificially opening a passage for the escape of the abnormal fluids; an incision is made into an abscess, puncture or a radical operation is performed in pleuritic exudations, the mastoid process is trephined, and so forth. Such a procedure is more especially to be commended in purulent exudations, since with a suppurating surface absorption is wont to be either completely suspended or reduced to a minimum. The material thus drawn off is, it is true, lost to the organism; and in this respect such a method of cure apparently falls short of that through absorption alone. Yet the importance of absorption must not be overrated. The fatty emulsion into which an exudation is transformed has certainly no greater value for the organism than belongs to any solution of albumen, fat, and salts of the same concentration. Thus the loss can be made good by increasing the supply of nourishment to a corresponding extent after the last remaining products of the disease have been disposed of by the operation. The gain to the organism from such a procedure is incomparably greater than the loss.

A therapeutic measure of this kind is the more clearly indicated, wherever at all possible, as exudations may meet with a worse fate than slow absorption. In exudations of some magnitude it is by no means uncommon for the transformation into a fatty emulsion to cease after a time, whereupon the liquid, but not the solid portion of the exudation is absorbed. The exudation then becomes *inspissated*, and is transformed *into a yellowish-white, tenacious, more or less dry mass* of the consistency of soft, oily cheese. When this change has occurred further absorption is practically impossible. On the contrary, the caseous masses—which are not to be confounded with the caseous products of tubercle and scrofula—themselves generally act as foreign bodies, and excite a fresh inflammation around them. During the course of the inflammation a kind of capsule is formed as the result of processes which will shortly occupy our attention more closely. But the inspissation need not even stop here; the soft mass becomes firmer; lime salts may be deposited, and lead to the formation of *chalky, mortar-like concretions*. In themselves the inspissated exudations are comparatively harmless, especially when calcified, any infective organisms that may have been present having long since perished. Yet their bulk alone may make them injuriously burdensome. Still more important,—the presence of such encapsuled, inspissated exudations renders a complete *restitutio in integrum* impossible. They remain as *loci minoris resistentiæ*, in which on slight provocation a fresh inflammation may at any moment be developed.

When, however, the exudation is the product of an *infective* inflammation, whether this character has belonged to it from the first or been subsequently acquired, the removal of the exudation by operation is of still greater importance. For, in the first place, the inflammation here serves as a *focus of infection*, whence there proceeds that action on the centres controlling the bodily temperature which leads to pyrexia, while, in the second place—and this is of more concern at present—*new inflammations having analogous characters* are induced by it. These secondary inflammations, unlike the metastatic form previously discussed, are seated in the first instance *in the immediate neighbourhood* of the primary focus. Under this head comes the implication of the pericardium in pleuritis, as well as the pleuritis supervening on peritonitis; and in the same category must be placed that form of erysipelas which, under the name of *progressive phlegmon*, is so justly dreaded, also the purulent inflammation so often arising around a suppurating joint without perforation of the capsule, as well as the secondary arthritis occurring in erysipelas of the periarticular tissues. But the commonest example is presented by the extension of the inflammation along the *lymphatics*, and the secondary inflammatory swelling of the *lymphatic glands* into which the implicated vessels discharge their lymph. The peculiarity of these inflammations in which a *phlogogenic poison*,* as it is called, develops, has long been familiar to physicians. The inflammation set up around a simple fracture is never *progressive*, nor is there any danger that an erysipelas due to a burn, or a keratitis produced by a caustic may become so. You will not confound this progressive character with the tendency of an inflammation to spread equally in all directions around, say, an eschar, for in the latter the disturbance becomes gradually less marked from the centre towards the circumference; in the progressive creeping inflammation, on the contrary, the same severe and pernicious characters are invariably displayed, no matter what the distance from the original focus may be. We may therefore conclude that this phlogogenic capacity is altogether unconnected with the simple products of inflammation, a conclusion which is borne out by the consideration that it would be impossible to understand how materials which a moment before had been constituents of the normal circulating blood should prove so dangerous on leaving the vessels. But I have already indicated wherein the essence of the processes consists; *they are infective inflammations whose pro-*

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* Virchow, 'Ges. Abhdl.,' p. 703; Billroth, 'Allgem. chir. Pathol. u. Therapie;' "Ueber d. Verbreitungswege d. entzdl. Processe," Volkmann's 'Vorträge,' No. 4; 'Untersuchungen über Coccobacteria septica,' Berlin, 1874.

ducts act infectively. Since, however, we convinced ourselves when considering the causes of inflammation that the parasitic theory stands in by far the closest correspondence with facts, it is but a step to the assumption that bacteria, or the decompositions set up by them, are the agents in the progressive inflammations also. Nor does this assumption rest on merely hypothetical grounds. The keratitis originating in a simple injury to the cornea, or produced by passing a clean thread through its substance, never attains any great dimensions, but soon begins to heal after the thread has been expelled, or the epithelial covering restored, as the case may be. But if at the same time the wound be inoculated with septic material containing bacteria, a severe inflammation with *a pronounced tendency to spread* is rapidly developed, hypopyon is readily set up, iritis and choroiditis may become associated with it, and even complete panophthalmitis supervene.* I remind you further of wound-erysipelas, in which colonies of micrococci occupying the finest lymphatics and interstices of the skin have been observed by Lukomsky.† Their presence could always be more certainly counted on in the parts most recently affected or in the tissues which, immediately bordering on the latter, would presumably be the next to become involved in the process. But perhaps the most convincing example of bacterial influence in these progressive inflammations is afforded by *pyelonephritis*. For here, as was first pointed out by Klebs,‡ we never fail to discover *colonies of micrococci in the urinary tubules,* where the inflammation is still recent and less advanced. To this point, though opposed by the flow of the secretion, they have travelled along pre-formed paths, and wherever they have gone inflammation has accompanied them. You will not have failed to notice how well the assumption of bacterial agency harmonises with the idea that the propagation of an inflammation takes place along the course of the lymphatics and lymph-spaces of the connective tissues. It is certain, then, that in a number of the progressive inflammations *the extension of the disease is*

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* Stromeyer, 'Med. Ctbl.,' 1873, No. 21; Arch. f. Ophthalm.,' xix, Abth. 2, p. 1, xxii, Abth. 2, p. 101.

† Lukomsky, 'Virch. A.,' lx, p. 418.

‡ Klebs, 'Hdb. d. path. Anat.,' Bd. i, p. 654.

effected by micro-organisms; in the remainder a similar explanation is at least, you will admit, a very legitimate hypothesis, for, should you not accept it, you must have recourse to other much more obscure chemical decompositions, by which the inflammatory product could acquire its phlogogenic character. But whatever be your interpretation of these processes, it is at any rate certain that, as has been dwelt upon more than once, they belong to the domain of the infective inflammations, and this being so, it is easy to understand how it happens that we have to deal in the vast majority of cases with suppurative processes. Pyelonephritis is a typically suppurative inflammation; in progressive keratitis suppuration of the whole eyeball often occurs, and no other kind of peritonitis is so liable to involve the pleura as the suppurative form. It has already been stated that the inflammations of the joints and cellular tissues, in which an insidious extension of the disease is so greatly to be apprehended, and which are so commonly attended by lymphangitis, belong to the suppurative class. In view of these facts, I need hardly enter upon a detailed discussion of the advantages accruing to the organism from the removal by operation of such inflammatory products. Clearly the earlier they are got rid of the better; the physician should *prevent* further infection wherever it is possible to do so. But even when we have to deal with an abscess whose phlogogenic character is no longer doubtful, and which has already, perhaps, given evidence of its nature, the removal of the pus is very desirable, inasmuch as absorption by the lymphatics, and infection of the lymphatic system, occurs more easily and certainly in proportion to the amount of tension to which the tissue-meshes are exposed through the presence of the inflammatory infiltration.

If the operative removal of the inflammatory products now under discussion were only always possible! True, the purely surgical inflammations, phlegmonous erysipelas, suppurations in joints, &c., do not usually present any difficulty. The occurrence of puerperal peritonitis, as well as its extension to the pleura, may also occasionally be prevented by operative treatment of the phlegmonous parametritis. But to bar the advance of purulent pyelitis to the kidney, and thus to avoid the development of a pyelonephritis,—to effect this, the physician, despite all the progress made by our art, is still practically powerless. The same applies with still greater force to the so-called *secondary inflammations*, which belong exclusively to the province of internal medicine. A true croupous pneumonia may lead to fibrinous pleuritis—a result which comes under the head of inflammation spreading by continuity, but it may also be complicated by nephritis or by meningitis. And although it might be said that the kidneys inflame because the infective poison is eliminated from the body by these organs, an attempted explanation of this kind does not meet the case of the pia mater. Yet here we have a true inflammation in no way distinguishable from a primary or epidemic meningitis, and unless one is satisfied to adopt a most improbable hypothesis, and to assume in so many cases that the same individual is first infected with the virus of pneumonia, and then with that of nephritis or arachnitis—that we have to deal with accidental combinations of independent, wholly unrelated, infective diseases—there remains, so far as I see, nothing for it but the view I have just announced. The nephritis, endocarditis, or meningitis, which supervenes on pneumonia, is a *secondary*, or (to employ a favourite *terminus technicus*) a *metastatic* inflammation, and is therefore the complete analogue of the orchitis which sets in in the course of mumps, or of the inflammation of the knee-joint which occurs during an attack of urethritis and cystitis. I have good reason for mentioning the last-named metastases expressly, since, though long known to us, they are seemingly highly peculiar and isolated phenomena, and as such have often been regarded with scepticism. At present they are completely divested of their striking characters, and no one now doubts the causal connection of the two affections respectively. Have I not recently dwelt on the fact that, so far from having such doubts strengthened, we are daily learning to see how many inflammations, formerly regarded as independent, originate as secondary affections in the course of infective processes? The complete elucidation of this relationship is allotted chiefly to the clinician, who has the patient's clinical history at his disposal. Yet pathological anatomy is also in a position to contribute something towards the same object—and this over and above the decisive evidence it may supply of the possible presence of organisms identical with those of the primary disease. Thus, for example, the great frequency of valvular disease in individuals who have never suffered from rheumatic fever will appear perfectly credible to anyone who knows how extraordinarily common it is to find a wreath of fine warty excrescences, occupying the line of closure of the mitral or aortic valves, in the bodies of persons who have died of some acute or chronic infective disease, such as typhoid fever, ulcerative pulmonary tuberculosis, smallpox, septic processes, &c., although no symptom had pointed to the existence of a cardiac lesion during life. But however clearly we recognise the intimate connection between the secondary inflammations and the primary disease, and the dependence of the former on the latter, it is only too manifest that—in spite of the enterprising spirit of a few surgeons,* any operative interference with the primary affection is impracticable. Accordingly, it is the natural process of absorption that must in these cases bring about the removal of the inflammatory products.

Everything I have so far said with regard to the course of inflammation has concerned exclusively the history of the vessels, and of the transudation, which is produced by the vessels during inflammation. No fundamental objection could be raised to my confining myself on the present occasion within these limits; and I might defer the account of the events occurring in the tissues during inflammation till we come to deal with the pathology of tissue-metabolism. If I, nevertheless, anticipate matters, and enter somewhat more minutely into these events, it is principally for practical reasons, for the prevention of errors and misconceptions, in which this, perhaps more than any other point in the entire doctrine of inflammation, has become involved. Inasmuch as the great majority of all inflammations, and more especially those which are produced experimentally, are wont to be combined with tissue changes of the most various kinds, the opinion has long prevailed that these changes form an integral part of the proper inflammatory process. And yet nothing could be more erroneous than this view. For the changes in question represent chiefly the mere damage done to the extra-vascular tissues by the exciter of inflammation. That such must ensue in many cases I have already had occasion to point out (p. 287). I need only remind you, therefore—to avoid repetition—how much importance we attached to necrosis of the tissues as a cause of traumatic inflammation. Thus it is something very common to meet at the seat of inflammation with cells whose protoplasm has become rigid, and whose processes are retracted or torn off, while their nuclei have disintegrated and vacuoles formed in the cell contents, and the like. How little essential connection there is between these appearances and the inflammation cannot anywhere be more strikingly demonstrated than in the non-vascular tissues, which have, nevertheless, so often and so long been made use of to prove the inflammatory nature of the tissue changes. For while such alterations are altogether wanting in the severe keratitis induced, after a few days, by passing a thread through the eyeball, the corneal corpuscles being in this case unaffected, most typical changes of the kind may be produced by cautiously applying a caustic to the centre of the cornea, and this without the slightest injection of the peripheral vessels to indicate that inflammation has even commenced. Such obvious changes in the tissue-cells cannot, it is true, be expected except after the operation of a specially severe form of trauma; and for the identification of a necrosis due to the cause of inflammation it is often necessary to employ careful histological methods, and the most delicate reagents. When, however, these are employed, one quickly becomes convinced of the great and unmistakable service done by Weigert in pointing out repeatedly and emphatically the extensive distribution of these *primary lesions of the tissues.** You know, too, that the necroses present in inflamed parts need not all be primary, for I have more than once dwelt upon the injurious influence which severe circulatory disturbance must exert on the nutrition of the tissue-cells. This influence is perhaps less frequently manifested by complete necrosis than by certain chemical changes, or, as they are commonly called, *degenerations.* Fatty degeneration, for example, is an extremely frequent occurrence during the course of an inflammation. Yet these degenerative processes are but too often the prelude to complete destruction.

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* Hueter, 'D. Zeitschr. f. Chir.,' ix, p. 427.

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* Weigert, 'D. Pockenefflorescenz d. äusseren Haut.,' Breslau, 1874; 'Ueber pockenähnliche Gebilde in parenchymatösen Organen u. deren Beziehung zu Bacteriencolonien,' Breslau, 1875; 'Virch. A.,' lxx, p. 461, lxxii, p. 218, and especially the article "Entzündung" referred to in note, p. 328.

In any case, however, the necroses are the most important of the tissue changes occurring in the course of inflammation; if for no other reason because they give the impulse to processes which, to my thinking, are calculated to excite a much higher degree of interest, namely, the *processes of regeneration.* You are perfectly familiar with the conception that the human organism is not a stable machine, remaining unchanged in structure and composition, and that so long as the individual lives, there incessantly takes place a waste of the constituents of the body, on the one hand, and a repair of this waste on the other. True, there is the greatest difference not only in the amount, but also in the kind, of waste and repair, according to the organ in which they occur; and I am far from saying that the *form* of the constituent tissue-elements is everywhere affected by the waste. But where this is the case, as in the epidermis and the compound epithelia, the blood, lymphatic glands, and spleen, there occurs, *pari passu* with the waste and loss, a new formation of elements, which —except during the period of growth—is always *just sufficient to cover the loss.* Yet I should hesitate to deduce from this a general law to the effect that the amount of new formation is directly dependent on, and determined by, the amount of waste; for waste and repair have their special conditions, which are probably very complicated, and which we are still very far from grasping *in toto.* But whatever may be the hidden causes of these processes, it is at any rate certain that in healthy and normal individuals waste and repair counterbalance each other on the whole. And this holds true not merely when the waste remains within strictly physiological limits, but also when it is for any reason increased. A hair which has been cut grows henceforward more rapidly than it otherwise would; and on an abnormal loss of blood there follows forthwith an abnormally active blood-formation. Precisely the same rule applies to the loss of substance produced through destruction of the tissue-cells by the exciter of inflammation or by some agency or other during the course of the affection; here too a *correspondingly increased regeneration* follows. The regeneration is, it is true, more abundant, but it takes place in a manner exactly resembling physiological repair; wherever it has been possible up to the present to follow the morphological details of this interesting process, it has turned out that the new elements are derived from old ones having the same characters. This has been known for a considerable time of the *epithelia*;[*] it is also true of *muscles*[†] and *nerves*.[‡] The restoration of the osseous tissue, *e.g.* the formation of callus after a fracture, devolves on the *periosteum*, the membrane which in the adult is entrusted with the production of bone. But there is no more favorable field for the study of these regenerative processes than the *cornea*; because we cannot so certainly succeed elsewhere in causing considerable loss of substance, and in, at the same time, completely excluding inflammation. In fact it is precisely the anterior epithelium of the cornea that offers the most convenient opportunity for the successful study of epithelial regeneration; besides which, *the regeneration of the corneal corpuscles* has been traced in the first instance by Eberth,[§] and then with special care by Senftleben[||] in my institute at Breslau. The vast importance of these latter investigations consists, firstly, in their having proved that the corneal corpuscles are produced solely from other corneal corpuscles which have remained undestroyed in the neighbourhood of the defect or eschar; and, secondly, in their having accurately demonstrated the *entire want of*

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[*] Arnold, 'Virch. A.,' xlvi, p. 168; Thiersch, in 'Pitha-Billroth's Hdb.,' i, Abth. 2, p. 531; Cleland, 'Journal of Anat. and Phys.,' 1878, ii, p. 361; Wadsworth u. Eberth, 'Virch. A.,' li, p. 361; F. A. Hofmann, ibid., p. 373; Hejberg, 'Oest. med. Jahrb.,' 1871, p. 7; Klebs, 'A. f. exp. Path.,' iii, p. 125; Flemming, 'A. f. mikroskop. Anat.,' xviii, p. 347.

[†] Cf. Kraske, 'Experimentelle Untersuchungen über d. Regeneration d. quergestreiften Muskeln.,' Habilitationsschrift, Halle, 1878, containing numerous references to the literature of the subject.

[‡] Vide sec. iv, chap. vi, 'Regeneration.'

[§] Eberth, 'Virch. A.,' lxvii, p. 523; 'Untersuchungen aus d. pathol. Inst. zu Zürich,' Heft 2, 1874, p. 1.

[||] Senftleben, 'Virch. A.,' lxxii, p. 542.

dependence of this regeneration on the inflammation. For not till it had been shown that, when a caustic is applied to the cornea or a wound made in it, the proliferation of the fixed corneal corpuscles takes place in precisely the same manner, whether inflammation sets in or does not set in—only then, I say, was incontrovertible proof afforded that this process is *purely regenerative*, and has at bottom no connection with the process of inflammation, to which it had so long and so universally been attributed. This is the true state of the case; in spite of the extraordinary frequency, I might almost say constancy, with which these changes are observed in inflamed tissues, they are nothing but complications of the proper inflammatory process. More than this, it may even be questioned whether the presence of inflammation furthers the proliferation of the tissue-cells. There is at any rate no necessity for its presence; and it is safe to assert that in the severe purulent and hæmorrhagic forms it is not merely no aid, but rather an impediment. The slowness and feebleness with which the production of callus and the regeneration of muscle is often effected in compound fractures, when extensive suppuration has set in in the limb, is an old experience. Of the ordinary, non-suppurative inflammations we cannot, however, speak so unfavorably. On the contrary, it seems to me quite allowable and justifiable to refer to the *inflammatory hyperæmia* as explaining an occurrence, which is very often observed in the regenerative proliferation of inflammation, namely, the *superabundant formation of tissue.* This over-production is evident in the exuberant epithelial proliferation occurring during inflammation, as well as in the connective-tissue cicatrices which are at first so prone to project as red eminences above the level of the skin. Nowhere, however, is it more striking than in inflammatory regeneration of bone, where far more callus is regularly produced than is required to replace the parts that have been lost through necrosis.

But however considerable the results of regenerative proliferation under certain circumstances may be, the process is very far from always terminating in the restoration of the part. The regenerative capacity of man and of the higher classes of animals is in itself restricted; so that the restoration of composite organs and apparatus, which in reptiles, for example, is successfully effected, is here altogether out of the question; the regeneration of the tissues and their elements being the utmost that can occur. Yet it is not every tissue even that is capable of restoration, *e. g.* the parts of the *central nervous system* can never be restored. In the case of many glands also, *e. g.* the liver and kidneys, all attempts at obtaining an accurate knowledge of the details of the regeneration of the specific cells have hitherto failed; although I should by no means conclude from this that regeneration is therefore impossible here. But even in tissues about whose regenerative capacity there is no doubt, restoration may fail to occur, or may remain defective, not only when the process is directly interfered with by some factor or other, *e. g.* by the suppurative character of the inflammation, but also and chiefly when the amount and extent of the defect exceed the reparative powers of the organism. In both cases, however, an imperfectly filled defect remains; and there then comes into operation the principle which, so far as I know, was first recognised and formulated by His with respect to embryological development, namely *that into all regions not occupied by specific tissues a vascular connective tissue grows.* While accordingly the importance of the formation of connective tissue in inflammation is sufficiently apparent, it becomes very much greater in view of the fact that in all lesions of the connective tissue itself, its office is to effect direct regeneration. Anyone who attaches special value to nomenclature as a means of indicating the principles he adopts, may, by way of contrast to this true and *perfect regeneration*, regard the formation of connective tissue in place of a specific tissue as *imperfect regeneration.* At any rate, it is more important to understand the process by which the formation of connective tissue is effected in each case. In one respect this termination of inflammation is directly opposed to all other modes. In the forms previously discussed, the inflammatory products, whatever their character and the changes undergone by them, never became integral and functional constituents of the body. Here, however, we have a tissue which is in no way distinguishable from the analagous tissue found in other parts, and which but too often proclaims its vitality to the detriment of the organism. It is, therefore, with good reason that this form of inflammation has received the name *productive*. In saying which, I desire to give prominence to the fact that we have not here to deal with an inflammation, the product of which is the simple equivalent of the other forms of exudation. The development of connective tissue represents, as already stated, *a termination of inflammation*, which may occur in any form of the affection when sufficiently active and prolonged—with the reservation that the production of connective tissue, like the true regenerative proliferation, is usually very much reduced in cases of deep and severe suppuration. How it happens that exudations so different in form tend to terminate in the same manner can be best appreciated by you, if I attempt to lay before you whatever of a certainly established character is known of productive inflammation or of the accompanying tissue-formation.

The dominant and directly determining factor in the entire process is the *new formation of blood-vessels*. Nothing more clearly proves the truth of this rule than the history of the extravasated cells in cases where *the vessels fail to be formed*. I mean, of course, the colourless cells; for no one will suppose the red blood-corpuscles to be capable of taking any part in the formation of the new tissues; and just as little will anyone be likely to attribute this capacity to the fibrin, *i. e.* to the product of the disintegration or solution of certain colourless cells. But on recalling the facts already referred to with regard to the fate of the colourless corpuscles in the inflammatory product, you will remember that I hinted at the probability of a multiplication by division of the corpuscles contained in the exudation. We are in possession of statements to this effect by several authors, as for instance Stricker, Ranvier,* who say they have now and then succeeded in directly observing the process of division under the microscope. Though their observations, it is true, do not altogether meet the morphological requirements we now make before admitting the occurrence of division, yet they are still valuable. The division of a cell does not, however, appear to be a very common event, if one may venture to judge of its frequency from the circumstance that the great majority of observers have failed to detect it, even after sufficiently prolonged observation. However this may be, the question whether the number of pus-corpuscles present in an exudation can be increased by division, though interesting from the standpoint of general morphology, is of very subordinate importance so far as the comprehension of the process of inflammation is concerned. For it is in the end immaterial whether the pus-corpuscles are already fully formed at the time of their passage through the vessel walls, or divide after extravasation into new ones, which are built up by the assimilation of substances supplied them by the vessels; this amounts merely to a change in the place of their manufacture. While, then, the alleged multiplication of the exudation-corpuscles by division is not a real addition to our knowledge of the process in its essence, this is still further from being the case with the *fatty degeneration* already familiar to us. Rather, we learned to regard the latter as a preliminary to the transformation into a fatty emulsion, *i. e.* towards disintegration, and this metamorphosis of the pus-corpuscles no more aids in tissue-production than does the shrivelling and drying of the same elements during the caseous inspissation of an exudation. Hence if the possible fate of the pus-corpuscles in inflammatory products were confined to these changes, but little weight indeed could be given to their claim to take part in tissue-production. But if you place under the microscope a drop of fluid, obtained either from a wound which has been granulating for about a week, or from a circumscribed exudation in the abdominal cavity or subcutaneous tissue of about the same age, you will find multitudes of ordinary, and some fatty, corpuscles, and among them, as a rule, a limited number of other structures. The latter are considerably *larger* than pus-corpuscles, and vary in shape, being globular, elliptical, or irregular; some of them contain *one* large nucleus, others more than one, and a few are even possessed of several; some are pale and finely granular, while in others the granules are larger. How are these structures to be explained, and where do they originate? They cannot be derived from the blood, from the vessels, simply because their counterparts are never found there. They must have arisen outside the vessels; and since they are met with only in the inflammatory product, and are constantly present in it in all parts of the body, we are involuntarily compelled to adopt the hypothesis that it is to the pus-corpuscles they owe their origin.

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* Stricker, 'Studien d. Inst. f. exp. Path.,' p. 18. Division of the white blood-corpuscles was observed by Ranvier in the axolotl, 'Arch. d. phys.,' 1875, p. 1, and by Klein in the triton, the frog, and in man, 'Med. Cbl.,' 1870, p. 17; cf. Fleming, 'Virch. A.,' lxxvii, p. 1.

The attempt to discover the genesis of these large cells must of necessity be attended by much greater difficulties than was the tracing out of the other events occurring in inflammation. For while in the latter we had to do essentially with processes which run their course with comparative rapidity, and never occupy a longer period than admits of an uninterrupted microscopic examination, much more time is necessary for the formation of the large uni- or multinucleated cells—six or eight days, or it may be more. But there is a further difficulty. In the cold-blooded animals, especially in the frog, the development of the cell-forms in question is far less constant and abundant than in the warm-blooded animals; and, indeed, a true formation of tissue as the result of inflammation hardly ever occurs in the frog. Yet only in this animal has it up to the present been found possible to carry out for any length of time a microscopic observation of the circulation which shall be free from errors. For this reason we are driven in greater part to construct the history of the new formations in question from a study of the finished products; and it was only to be expected that many gratuitous assumptions should creep into the interpretation of these processes. Here, again, it is by experiment that a foundation, in some degree secure, has been laid. In its application to this subject Ziegler* appears to me to have been most happy. He introduced small capillary chambers of glass, open at the sides, into the subcutaneous cellular tissue of strong dogs, and determined at fixed intervals the changes undergone by the colourless blood-corpuscles which had quickly entered the glass chambers. As regards the first stages,—those concerned with the development, that is to say, of the oft-mentioned large cells,—there are several experiments, some of them much older, which happily corroborate and supplement the researches of Ziegler; as, for example, those of B. Heidenhain.* More recently the process has been still further elucidated, in some of its aspects, by experiments carried out in my institute at Breslau by Senftleben and here by Tillmanns.†

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* Ziegler, 'Experiment. Untersuchungen über d. Tuberkelelemente,' Würzburg, 1875; 'Untersuchungen über pathol. Bindegewebs- und Gefässneubildung,' Würzburg, 1876.

The earliest examples of cells exceeding the ordinary pus-corpuscles in size make their appearance in the exudation, according to the unanimous statements of all observers, which my own experience goes to confirm, about the fifth day from the commencement of the inflammation, and thenceforward they steadily increase in numbers. At first they exceed the pus-corpuscles by from one and a half times to twice the size of the latter; are roundish, evidently contractile; but the energy of their amœboid movements is considerably less than that of the leucocytes. Their habitus and intimate constitution is variable, owing in great part, it would appear, to the difference in the material by the consumption of which their growth has been effected. If you introduce into the abdominal cavity of a rabbit a small linen bag filled with a few drops of moist vermilion, such as is contained in a painter's colour-box, you will find after about a week has elapsed, in the immediate neighbourhood of the little bag and between the threads of the linen, a very considerable number of large cells containing vermilion, together with a few pale ones. In like manner Senftleben, who experimented by injecting a dead cornea with a neutral solution of carmine, and then introducing it into the abdominal cavity of a rabbit, met after the same period with *large cells containing carmine*. Similar cells are of course present in the cornea of a living animal when slight inflammation has been set up by the injection of the same carmine solution. Moreover, when a circumscribed inflammation of the peritoneum is produced by the introduction of a piece of brain-substance, the large cells contain drops of unmistakable *myelin*. In short, the *pus-corpuscles grow by taking up whatever substances they find ready to hand.* That mode of growth upon which Ziegler, I believe correctly, lays special stress, namely, the enlargement of individual corpuscles by the consumption of others, is but a special application of this principle. For, according to Ziegler, the large cells arise in this way in the ordinary exudations where no other well-characterised substances and objects are at the disposal of the pus-corpuscles. He did not actually observe, it is true, the enlargement of some pus-corpuscles at the expense of others; yet his method of experimenting was such as to preclude all doubt that the large cells are derived from the leucocytes; and when it is considered in addition that the later he examined his chambers the fewer were the typical pus-corpuscles, and the greater the number of large cells, we can hardly hesitate to accept his conclusion. If, then, we have not so far succeeded in directly observing the origin of the large cells, you will hardly be surprised to learn that we are still far from possessing an adequate knowledge of the fate of the nuclei. In some of the large cells no trace of a nucleus is discoverable, in others the nucleus is pale and indistinct; others, again, have a more granular, clearly perceptible nucleus; while the majority—those, that is to say, which may be regarded as the type of these large cells—have one, rarely two, large clear nuclei with nucleoli. As to the origin of these large nuclei, which give the cells a striking resemblance to *epithelioid bodies*, we have at present no knowledge whatever. The protoplasm of the epithelioid cells is always finely granular and faintly glistening.

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* B. Heidenhain, 'Ueber die Verfettung fremder Körper in der Bauchhöhle lebender Thiere,' I.-D. Breslau, 1872; Langhans, 'Virch. A.,' xlix, p. 66; Rustizky, 'Virch. A.,' lix, p. 202; Köster, 'Virch. A.,' xlviii, p. 95.

† Senftleben, 'Virch. A.,' lxxii, p. 542; cf. also ibid., lxxvii, p. 420; Tillmanns, ibid., lxxviii, p. 437.

But the growth of the epithelioid bodies in the exudation does not terminate with the production of cells exceeding the pus-corpuscles by about twice the diameter of the latter. Towards the tenth or twelfth day much larger cells are constantly found, and these are still more numerous after the second week. They vary in form, being sometimes round, sometimes club-shaped, or furnished with truncated prolongations running in various directions; while in point of size they must be regarded as exquisite examples of *giant-cells*, which they moreover resemble in frequently containing a large number of nuclei, ten, twenty, or even more.

B. Heidenhain found that pieces of elder-pith, introduced into the abdominal cavity of the guinea-pig, contained very large and beautiful giant-cells after four weeks had elapsed. Ziegler determined their presence in his glass chambers at a much later date, but also met with them as early as the twelfth day. Besides these immense giant-cells, smaller forms are always present; so that, in fact, all the transitional stages between the epithelioid and the giant-cell may be readily demonstrated. Similar transitions in the number of cell-nuclei are also observable. Such being the case, it may fairly be assumed that the giant-cells are built up by the gradual consumption of other materials, in particular of exudation-corpuscles. According to this view they develop by the blending of several pus-corpuscles in succession, which, ceasing to lead a separate existence, become completely merged in and assimilated the one by the other. Hence they distinctly contrast with those forms, frequently of great size, where a number of distinct pus-corpuscles occupy the interior of a large cell—forms which not so long since were supposed to be mother-cells* of pus-corpuscles, but which now-a-days are looked upon rather as products of the inclusion of some of the pus-corpuscles within others.

But however large the cells of an exudation may grow, and however surprising the forms which result, their continued existence is impossible, *unless a new formation of blood-vessels comes to their aid.* If blood-vessels are not formed, these structures all succumb sooner or later to the inevitable fatty degeneration, just as do the ordinary pus-corpuscles. At the time of the first appearance of the epithelioid cells, a number of pus-corpuscles have already degenerated; a few days later, and isolated fat-droplets are found in the large cells, which now gradually become transformed into the prettiest Gluge's corpuscles. The same may be observed in the giant-cells. Fatty degeneration is but the prelude to disintegration, as the result of which the cells, formerly so flourishing, are reduced to be mere constituents of a fatty emulsion. Considering the rapidity with which the fatty degeneration of the pus-cells passes on into disintegration, the fact that such large numbers of epithelioid and giant-cells continue for so long a period to contain droplets of fat would indeed be remarkable, were it not possible for the latter to be derived from an entirely different source. Since, as has just been shown, the pus-corpuscles and their derivatives, *i. e.* the epithelioid and giant-cells, consume such substances as are at hand, nothing could be more natural than that they should incorporate fatty material also. If you inject a fine oil-emulsion into the lymph-sac of a frog, you will find there after a few days the prettiest and most magnificent Gluge's corpuscles; and the same result has been observed by Wegner,* who injected oil into the abdomen of rabbits. Hardly less rapid is the formation of these inflammatory corpuscles when disintegrated or necrotic nerve-tissue is exposed to the action of pus-cells. Senftleben† found that on waiting a few additional days before removing the pieces of brain-substance from the abdomen, he obtained fat-droplets in the large cells in place of the characteristic drops of myelin; and there is not the least doubt that the much-debated compound inflammatory corpuscles, which appear with such constancy in inflammation, softening, and degeneration of the central nervous system, originate solely by *the inclusion of disintegrated nerve-substance*, chiefly of the white substance of Schwann, *in and by lymph- or colourless blood-cells*. But identical corpuscles are often present in very large numbers in inflammations of the subcutaneous cellular tissue or of the abdominal cavity, where no white substance exists; and Ziegler met with them in his glass chambers. Yet here too their formation is very easily accounted for; in the fattily degenerated pus-corpuscles a most excellent material is provided for consumption, and we may certainly attribute the production of a considerable proportion of the large corpuscles of Gluge to the simple fact that fattily degenerated cells have been devoured by others. This applies not only to the commonest form of Gluge's corpuscles, which corresponds in size to the epithelioid cell, and which, being provided as a rule with a large clear nucleus, may be properly regarded as a coarsely granular modification of it; all that has been said applies equally to the coarsely granular giant-cells containing fat-droplets. No more beautiful examples of the latter are anywhere met with than those occurring in somewhat old foci of brain-softening, or in the immediate vicinity of pieces of dead brain-matter which have lain for two or three weeks in the abdominal cavity of a guinea-pig or rabbit. The epithelioid and giant-cells containing fat-droplets are, accordingly, to be grouped in two different classes; yet this does not alter the fact that none of these cell-forms can undergo further development unless new blood vessels are produced. In the absence of a blood-supply their inevitable lot is disintegration, shrivelling, inspissation, and the like.

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* Buhl, 'Virch. A.,' xvi, p. 168, xxi, p. 480; Remak, 'Virch. A.,' xx, p. 108; Böttcher, 'Virch. A.,' xxxix, p. 512; Bizozzero, 'Wien. med. Jahrb.,' 0.

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* Wegner, 'Langenbeck's A.,' xx, p. 51.

† Senftleben, 'Virch. A.,' lxxii, p. 542.

The question, *How does the new formation of blood-vessels take place?* although it has so long engaged the attention of anatomists and pathologists, awaits even to-day a final decision, so far at least as pathological vascularisation is concerned; because, as I already pointed out, all attempts at directly observing the process have heretofore miscarried. Yet such a mass of isolated facts and series of observations, all of them harmonising with one another, have been contributed from the most various quarters, that one may venture on a definite opinion, despite the deficiency just alluded to. In the first place it was determined by the earliest authors* *that the new vessels are outgrowths from the old*, and from that time until now this view has received every kind of confirmation.† Buds are formed, which shoot out laterally from the vessel wall, and gradually increase in length; similar buds given off from other vessels grow to meet these, and coalesce with them. The buds are at first *solid;* but they subsequently become tunnelled, while those portions of the vessel wall from which they have grown undergo liquefaction; and in this way new vascular offsets and loops arise. The fine vessels first formed are always capillaries, and are chiefly, though not exclusively, outgrowths from true capillaries. Later on they gradually become wider and acquire thicker walls, and may thus be transformed into vessels of large size. Such being the origin of the new vessels, the source of their blood-supply is at once evident; from the *general* circulation blood passes out of the old into the new channels. But other new vascular channels, not directly continuous with pre-existing blood-vessels, arise in inflammatory cell aggregations. This fact was also determined by very early observers, but authors still differ somewhat as to the history of their formation. According to some,[*] the exudation-cells arrange themselves side by side in parallel rows, become flattened into endothelial cells, and unite to form tubes; such channels would accordingly have an *intercellular* origin. In opposition to this view, many authors, especially the most modern, and amongst them Ziegler, hold that the formation of these vascular channels is *intracellular*. According to them, some of the large cells send out processes in one or more directions; these become pointed and increase in length till they impinge on vascular buds or fully formed vessels. Thereupon the cells and their processes undergo excavation, *canalisation*, and liquefaction of the vessel wall taking place at the point of junction, new vascular offsets and tubes are formed. The latter view is, at any rate, supported by the fact that all the events concerned in the new formation of vessels are by this conception brought under the same head, for in vascularisation by means of budding we are dealing with a growth and formation of processes in cells,—the cells comprised in the vessel-wall. Moreover, this view harmonises completely with the discovery of J. Arnold,[†] who found that in very young vessels the endothelial elements are not mapped out in the well known manner by treatment with nitrate of silver, and that differentiation does not take place till later, when the tubes are already fully formed; granular plates then making their appearance, which gradually clear up and become endothelial cells. However this may be, the blood flowing through these new vessels, whose junction with the previously existing ones is subsequently effected, also proceeds from the general circulation. At least, I have not succeeded in convincing myself of the correctness of the statement* that red blood-corpuscles arise independently in the interior of such newly formed vessels. On the contrary, I think I am justified in positively asserting that, in a keratitis vasculosa, an injection mass, if carefully introduced from the carotid, may be made to penetrate all the channels in which red blood-corpuscles are contained.

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* Jos. Meyer, 'Charité-Annalen,' iv, p. 41; Billroth, 'Untersuchungen über d. Entwicklung d. Blutgefässe,' 1856; C. O. Weber, 'Virch. A.,' xxix, p. 84.

† J. Arnold, 'Virch. A.,' liii, p. 70, liv, p. 1; Ziegler, 'Untersuchungen über pathol. Bindegewebs- und Gefässneubildung,' Würzburg, 1876; Tillmanns, l. c.

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[*] J. Meyer, Billroth, O. Weber, ll. cc.; His, 'Beitr. z. norm. und. path. Histologie der Hornhaut,' 1856.

[†] J. Arnold, 'Virch. A.,' liii, p. 70, liv, p. 1; Ziegler, 'Untersuchungen über pathol. Bindegewebs- und Gefässneubildung,' Würzburg, 1876; Tillmanns, l. c.

Now, how is it that the newly formed vessels supply such a strong stimulus to the further development of the exudation cells? No doubt by conveying to them an abundant supply of material specially adapted to their wants. But our certainty on this point makes the deficiency in our present knowledge of the circulation in the newly formed vessels all the more sensible. For since the subject has never been microscopically studied in the living animal with the circulation in progress, we are compelled to have recourse to mere hypothesis. True, the accumulation of red, and more especially of colourless, corpuscles in the interior of the new vessels, and the circumstance that in the neighbourhood of the latter there are contained at all times red corpuscles and a very large number of white ones—the latter often in densely packed rows—point with tolerable certainty to the conclusion that the *velocity of the stream* in the new vessels is *considerably lowered*, and that *a rapid extravasation of red, but above all of white, blood-corpuscles is taking place* without intermission. Yet these meagre facts merely suffice to explain how the loss of pus-corpuscles arising through their continued liquefaction and consumption by the large cells, is made good, and how the latter are constantly supplied with fresh material for assimilation. That the history of productive inflammation is fully elucidated thereby will be claimed by no one. Our knowledge of these processes is at present altogether confined to their purely morphological side; and even here many points remain to be cleared up.

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* Carmalt und Stricker, 'Wien. med. Jahrb.,' 1871, p. 428; Schaefer, 'Proceed. of the Royal Society,' 1872, No. 151.

It is certain that all further development depends on the epithelioid cells, compared with which the still larger giant-cells, being at all times much fewer in number, play a secondary part. The epithelioid cells, at first more or less round, send out processes later on, and so assume the spindle- or star-shape. These processes grow and undergo further metamorphoses, in which the characteristic element is the *splitting up into fine fibres and fibrillæ.* At one or both ends of a spindle-cell a tuft of fine wavy fibres is produced; while the broad surface may also be covered with numbers of fibrillæ by the differentiation of the cell protoplasm. By the union of the fibres of different cells there arise complete bundles of fibrillæ; which accordingly are contributed, as a rule, by several cells. The protoplasm remaining over from the fibrillæ goes to form the fixed cells, which occupy the spaces between the bundles. The entire process of development takes place within the supporting framework or network produced by the repeated anastomosis of the vascular arches; and the structure thus originated is *in summâ* nothing more or less than *true vascular connective tissue.*

Such are in brief the most essential features of the interesting and highly important process of tissue production in inflammation, as taught with the greatest accuracy and precision by the oft-mentioned researches of Ziegler. The further development of the giant-cells, if it occurs at all, takes place in an exactly similar manner. Many of them, however, perish in spite of the vascularisation; while to their growth, which is luxuriant in proportion to the poverty in vessels, vascularisation acts as a check. According to this view, the giant-cells are merely *hypertrophic* formative cells, the type of which is presented by the epithelioid elements; and this is quite consistent with the fact that the giant-cells may also, under certain circumstances, participate in the new formation of vessels.* The details which are disclosed by tracing from first to last the process, extending, it may be, over many weeks, are of course much more numerous than we can here refer to; and the study more especially of Ziegler's researches will make you acquainted with many very remarkable particulars, as well as with a number of variations. Yet, to the chief factors sufficient prominence has, I believe, been given. The circumstance to which Ziegler himself at least attaches chief importance is that the individual corpuscles are not engaged as such in building up the tissue, but that this is done by the larger uni- or multinucleated protoplasmic bodies arising from their coalescence, and above all by the epithelioid cells, which he therefore expressly designates *formative cells*. Accordingly, the fixed cells originating later are not the direct offspring of the pus-corpuscles, as believed by many authors,* but are formed from material which in its turn is derived from the colourless blood-corpuscles. If the entire doctrine, in which Ziegler is corroborated by some closely analogous facts of embryology, be correct, it throws a very striking light on a point formerly dwelt on, namely the unimportance of the supposed multiplication of pus-corpuscles by division in the exudation. The first step towards the organisation of the cells of an exudation is the coalescence of two or more to form one, *i. e.* a *falling-off* and not an increase in their numbers. Or are we to believe that nature, before advancing a step, takes one or more in a retrograde direction?

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* Brodowski, 'Virch. A.,' lxiii, p. 113.

With regard to the characters of the newly formed vascular connective tissue, the form assumed by it, and the degree to which it is developed, there may be the greatest variety according to the locality in which it is situated and the causes of the inflammation. The chief determining element is the *shape and extent of the defect* to the repair of which the connective tissue is applied. Very commonly a defect occurs in a connective tissue, which, being repaired by the same tissue, undergoes what we formerly called true and perfect regeneration. I cannot say whether, in addition to the new formation of connective tissue described above, there is another, so to speak, more physiological one; for of physiological waste and repair as it may occur in ordinary fibrous tissue our knowledge is most scanty, and we know nothing whatever of its amount. The formation of connective tissue just portrayed does not essentially differ in principle from the well-known processes of regeneration in specific tissues; for the new vessels are most of them here formed from the old ones, and the appropriation of extravasated blood-corpuscles to the formation of new connective-tissue cells would be deprived of its peculiarity should a view, in support of which many substantial grounds may even now be produced, finally prove to be true, and the fixed corpuscles of the normal connective tissue turn out to be the descendants, although perhaps only indirectly, of extravasated colourless blood-corpuscles. But however this may be, the want of similarity to the physiological process of regeneration is infinitely greater when the newly formed connective tissue takes the place of specific tissues that have perished; this, however, occurs, we have seen, only when the true regeneration of the latter for some reason fails. You will not expect the newly formed vascular connective tissue always to accommodate itself at once to the extent and configuration of the defect. Whether it does so or not depends on the continuance of the inflammation till the gap is filled out and its cessation at this point; and a special factor, which was already noticed in discussing the subject of true tissue-regeneration, is of importance here, namely *over-production*. It is something very common, I might almost say the rule, for a superabundance of blood-vessels, cells, and fibres to be developed in productive inflammation. Now if you consider, in addition, with what extreme frequency the new formation of connective tissue must, from the nature of the case, be associated with true regeneration, you will be convinced without further inquiry that the picture presented by productive inflammation must be an extraordinarily variable one.

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* Aufrecht, 'Virch. A.,' xliv, p. 180; M. Schede, 'Langenbeck's A.,' xv, p. 14; G. Bizozzero, 'Il Morgagni,' 1866, p. 49, 114, 253; Billroth, 'Oesterr. med. Jahrb.,' xviii, Heft 4 and 5.

To illustrate what has been said, let us take a particular case from among the more commonly occurring forms of inflammation; for example, a large *wound*, such as may arise through an accidental injury, the surgical extirpation of a considerable tumour, or a burn of higher degree. Here the simple exposure of so many vessels is certain to be followed by inflammation; and this continues, in the absence of complications, as long as any portion of the wound remains. The surface of the wound now goes on gradually diminishing, or, as it is called, heals over. This is effected simply by a *combination of regeneration with productive inflammation*. To the regenerative proliferation of the superficial epithelium of the skin the restoration of the epidermis is due; by which process it is true the more specialised epidermal structures, the hairs, sebaceous and sweat-glands, are usually left deficient. The new fibrous substratum which takes the place of the papillary bodies and subcutaneous cellular tissue is the result of the productive inflammation. Here too "over-production" is strikingly apparent, so that I was formerly able to select the "projecting red cicatrices" as typical examples of it. In all this, so far as we know at present, it is immaterial whether healing occurs under antiseptic precautions, or in the absence of such. True, in the latter case suppuration takes place, which in the former is absent; and its occurrence during the process of healing leads to the transformation of all the extravasated cells which come under the influence of the pus-poison into true multinuclear pus-corpuscles, with a consequent loss to the new formation. In antiseptic healing there is nothing to prevent their utilisation—it is quite possible, at least, that all extravasated corpuscles are utilised for the production of formative cells. Hence it is not difficult to understand how the formation of new tissue and the healing of the wound proceed much more rapidly and certainly under antiseptic treatment than when the surface is unprotected and suppurating. Yet in both cases it is obviously the same productive inflammation, the same new formation of vessels, on which the origin of the so-called *wound-granulations* depends; and it is by identical processes in the formative cells that the connective-tissue fibres are produced. In an ordinary *simple fracture*, on the contrary, the bone is more or less extensively broken; the periosteum, blood-vessels, and muscles are lacerated; the medulla, intermuscular, and subcutaneous cellular tissue crushed; and in addition blood and lymph are effused between the fragments of the tissues. That a mortification so extensive invariably leads to inflammation has already been stated. The inflammation is, it is true, mild in character; yet the activity of the extravasated blood-corpuscles both in effecting the resorption of the necrotic tissues, and in healing, is too important not to receive due recognition. While the effused blood and the mortified parts are being gradually absorbed and removed, repair has commenced, and here also true regeneration becomes associated with a productive inflammation leading to the formation of connective tissue. By true regeneration the periosteum, bone, and muscles are restored; by productive inflammation the intermuscular, periosteal, and subcutaneous connective tissues are reproduced; and the total result would be complete *restitutio in integrum*, were it not that a superabundance of callus is at first formed, which callus usually projects above the contour of the old bone, and encroaches on the medulla at the seat of fracture. But if for any reason true regeneration is prevented, or its energy considerably reduced, extensive connective-tissue callosities are formed between the muscular masses, and the ends of the fractured bone may even be united by a fibrous pseudarthrosis instead of by callus. The bands of cicatricial connective tissue met with in the *liver* and *kidney* may with still greater certainty be regarded as due to an inflammation, excited either by severe crushing or laceration, or by necrosis depending on infarct or some other cause. For that these masses of connective tissue have arisen solely by inflammatory new formation, and not by any metamorphosis of the specific parenchyma, has been indisputably proved for these organs by the experiments of Tillmanns.[*] Whether he injured pieces of dead liver and introduced them into the abdominal cavity of a rabbit, or wounded the organ in a living animal, he obtained the same fibrous cicatrices. The almost invariable success of his experiments throws at the same time a remarkable light on the absolute failure which attended his attempts in this institute to obtain a new formation of bone from dead periosteum or cartilage. The latter is a regenerative process, *i. e.* it is effected by the activity of special tissue-cells. The former is an inflammation, during which the special tissue-cells maintain a perfectly passive attitude.

The *cornea* also allows the relations of regenerative and inflammatory tissue-formation to be demonstrated very clearly. If you excise a large piece from its anterior surface, or cauterise it over a not too limited area with the red-hot button of a sound, injection of the sclerotic, and more especially of the peripheral, vessels is wont to set in very rapidly. Colourless blood-corpuscles penetrate directly, some from the periphery and some from the conjunctival sac, into the injured portion or into the tissues immediately bordering on the eschar, and here give rise to cloudiness. The regenerative proliferation of the anterior epithelium very soon commences, and after two days, at furthest, the entire surface of the wound is covered with newly formed epithelium; while, if the cautery has been employed and the eschar can be removed by constantly moistening it with liquid, the remaining defect rapidly receives an epithelial covering. As soon as this has occurred the inflammation quickly begins to subside; the pus-corpuscles that had invaded the cornea gradually disperse, as is demonstrated to the eye by the disappearance of the cloudiness; and the depression, which at first persists and may be clearly perceived on illumination from the side, also disappears during the succeeding weeks and months, owing to the regeneration, more or less energetic, of the corneal corpuscles and intercellular substance. If, on the other hand, the regeneration of the anterior epithelium is for any reason prevented, *e.g.* by a firmly lodged foreign body, the inflammation continues, and blood-vessels shoot in from the periphery of the cornea towards the seat of injury. A so-called *pannus vasculosus* arises, while in the inflamed area itself a connective-tissue cicatrix, or *leucoma*, is formed.

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[*] Senftleben, 'Virch. A.,' lxxii, p. 542; cf. also ibid., lxxvii, p. 420; Tillmanns, ibid., lxxviii, p. 437.

Turning our attention for a short time to the *serous membranes*, we notice that in severe inflammations a loss of tissue always occurs—it may be only of the endothelium, which is shed at a very early stage in every fibrinous inflammation. Supposing now the inflammation to continue for a considerable period, while the regeneration of the endothelium is delayed owing to the presence of the fibrin, vessels and vascular connective tissue will begin after a time to grow from the substance of the membrane into the cavity. When this takes place on two opposite surfaces, the newly formed masses of connective tissue may become united, and form band-like or filamentous adhesions, or shorter intergrowths. But union need not occur, and the process often stops short at the formation on the parietal or visceral layer of shaggy or fringed appendages, which cease growing when they have received, sooner or later, a covering of regenerated endothelium. It is essentially the same process which sets in when foreign bodies of any kind, *e.g.* Tillmanns' pieces of liver, are introduced into the abdominal cavity—except, of course, when a pus-poison is also present. The foreign body mechanically destroys the portion of the peritoneal endothelium in contact with it, and excites here a circumscribed peritonitis. Soon the new formation of connective tissue commences, and does not cease till the foreign body no longer touches an unprotected portion of the peritoneum, *i.e.* till it is completely enclosed in a connective-tissue *capsule*, and has in a sense been dislodged from its former position to one beneath the peritoneum. For as the regenerative proliferation proceeds, the external surface of the capsule, which is turned towards the peritoneal cavity, receives a complete coating of endothelium.

These examples will suffice, I think, to elucidate, as far as can be done at present, the essential, ever-recurring features of the productive inflammation, with its attendant tissue-formation. That the consequences of a productive inflammation to the organism may differ extremely can hardly have escaped your notice. True, it would not, in view of the wonderful adaptation of the organism to its ends, be a difficult task to show that the body could not react in a better or more advantageous manner to the noxa exciting inflammation than by the inflammatory disturbance of the circulation; yet our science has for so long a period been overwhelmed with discussions of this character that they have nowadays fallen into disrepute. But, granting the truth of the proposition, it does not follow that considerable disadvantage and danger may not attach to inflammation and its consequences, or that these may not even preponderate. We prefer, therefore, to confine ourselves to fact. It is, indeed, very satisfactory that a wound should cicatrise by granulation, or that a muscle when torn should unite in the same way; this is just as much a favorable event as that a fœtus or a fæcal concretion which has escaped into the abdomen should be there encapsuled. On the other hand, you are acquainted with the evil consequences which attend adhesion of the two layers of the pericardium, and it is easy to see that the fixation of one or more loops of intestine to the abdominal wall is very far indeed from promoting peristaltic action. It is unnecessary to describe how much vision is impaired when half or more of the cornea becomes covered with a connective-tissue membrane. But however greatly the significance and value to the body of these textural products may vary, they have one common characteristic, namely, absence of that solidity and invulnerability, if I may call it so, which so markedly distinguishes the old physiological connective tissues. The newly formed connective tissues remain specially exposed for a considerable time, and but a trifling injury is required to give rise to inflammation where they are concerned. But while the production of tissue in inflammation is of itself an extremely tedious process, the vulnerability of the newly formed tissue, and its liability to repeated attacks of disease, tends still more to impress on productive inflammation the character of tediousness, to convert it into what is called the *chronic* form.

You will certainly have noticed as an omission that I have paid little attention to the time occupied by inflammatory processes, although the division into an *acute* and *chronic* form is so greatly in vogue, perhaps, indeed, the most popular classification of all. My reason for attaching so little importance to these differences in time is that I am unable to perceive how the understanding of the processes in question can be facilitated by thus separating them. If you consider what has already been laid down by us on this point, you will at once remember how greatly the interval elapsing between the action of the cause and the outbreak of inflammation may vary. Immerse the paw of a dog or the ear of a rabbit in hot water, and after a few minutes the specific circulatory disturbance and the augmentation of transudation begin; and before a quarter of an hour has passed, all the cardinal symptoms are present *in optima forma*. If, on the other hand, you paint the paw with croton-oil; or, still better, introduce an infective plug into the median artery of a rabbit's ear, you will fail to perceive the slightest change in the vessels of the organ till after the lapse of several hours. But you are also acquainted with the cause of this difference. It depends solely on the time taken by the noxa exciting inflammation to reach the vessel walls, and on the period required by it to effect such an alteration as may result in an inflammatory disturbance of the circulation; whereby, it is true, the individual peculiarities of the vessel walls may also exert an influence in determining when the alteration shall be developed. Nor is it otherwise with its course subsequently. *As long as the cause is present the inflammation continues;* on the disappearance of its cause the inflammation quickly ceases, *i. e.* if recovery takes place at all. A burn of moderate degree always heals rapidly; and when a foreign body is expelled, or an eschar removed, the inflammation is soon at an end. A wounded surface, on the other hand, goes on granulating just as long as it is a wound; and if a foreign body is lodged at such a depth that it cannot be expelled the inflammation around it is very protracted. Another point is deserving of notice in this connection. To the persistence of the inflammation it is not necessary that the *original* exciting agent should keep on acting; the disease may also continue if, during the course of the inflammation (and it may be as the result of it), new noxæ, new causes of inflammation, come into operation. We have also become acquainted with good examples of the latter kind of process. The secondary infection of a wound-secretion, of an exudation, necessarily results in the persistence of the inflammation as long as the decompositions brought about by the infection continue. And although in these cases the infecting agent is something foreign, something supervening from without, it is not always so; I may remind you of the inspissated remains of exudations, with regard to which I formerly pointed out that they act as foreign bodies; and I may also remind you of the new-formation of vessels and of connective tissue, the dangers attending which I shall soon have to discuss more minutely. You see, we have not far to seek for causes which make it possible for an inflammation, at first *acute*, to persist, to become *chronic*. The nature of the process, however, is by no means changed; and as regards the alterations effected in the symptoms by the chronicity of the disease, these may be so easily inferred for individual cases that I need not stop to speak of them. But chronic inflammation can, and indeed very frequently does, originate in another way. Its symptoms may at first be so trifling that the commencement of the disease is quite unperceived, or else vaguely marked; and this is due either to its trifling *intensity*, or, what is more common, to the circumstance that in *extent* the process is at the start minimal. That slight inflammations of this kind are exceedingly common every-day occurrences there is not the least doubt. No attention is paid to them, and they really deserve none when they simply disappear. But under certain circumstances they do not disappear, or at most subside a little, only to undergo anew a slight exacerbation; then there arises in the vicinity a similar inflammation, in itself trifling, and runs a similar course, and so on. The final result must evidently be precisely the same as if an acute inflammation had become chronic, *i. e.* the affected part does not for a long period reassume its normal condition, a more or less permanent circulatory disturbance of moderate degree with all its consequences having become established in it. It is often hard to say subsequently what are the conditions under the influence of which these insidious chronic inflammations have developed. Not uncommonly it is to frequently recurring noxæ, trifling in themselves, that many a chronic rheumatism, catarrh, nephritis or hepatitis must be referred. But nothing so favours this chronic course as certain general, so-called constitutional diseases, like *tuberculosis*, *syphilis*, &c., to which again the rule that the essential, ultimate cause of inflammation is of a *persistent* character is perfectly applicable.

As to what inflammations should be included under the term chronic, you will not expect that cases in which the disease stops short before a tumor is produced, or perhaps goes on to the formation of a serous exudation, will last long enough to be regarded as chronic, so that when, for example, on puncturing a pleuritic effusion of old standing, a clear serous fluid is almost the only thing obtained, you may be absolutely certain that more or less extensive fibrinous deposits remain within the thorax on the surfaces of the pleura. But exquisitely chronic *purulent* inflammations occur, and here too in both forms,—that arising out of an acute inflammation, *e. g.* a chronic empyema, and that setting in insidiously from the first, as the abscesses of glanders and the so-called chronic pyæmia. To the same category belong the much discussed *cold abscesses*, in which, as the name implies, one criterion of acute inflammations, the calor, is greatly reduced or altogether absent. At this stage of our discussion I need hardly point out what this "coldness" indicates, for you know that the temperature of an inflammatory focus can never fall below that natural to the affected part in a normal state, except when the retardation of the blood-stream through its vessels preponderates over the increased supply brought about by the vascular dilatation, *i. e.* the hyperæmia. This also explains how it is that this chronic suppuration cannot well lead to a new formation of vessels and tissue. The most important, and, if you will, most typical form of chronic inflammation is therefore the *productive*, or, as it is also termed, the *adhesive*, whether it originates in the simple, interstitial, fibrinous, or purulent variety. The manner in which such a productive inflammation is developed from an acute one has just been minutely discussed, and it need hardly be added that in the insidious cases also the adhesions, thickenings, and callosities are invariably due to small exudations.

I have already more than once hinted at my reason for regarding *adhesive* inflammation as the most typical chronic form. It is the fact, confirmed by innumerable experiences, that the newly formed vessels and tissues themselves constitute *fresh causes of inflammation*. At any rate they may become so; for the most trifling noxa at once alters the flow through them, and immediately leads to a renewal of the transudation and extravasation. Moreover, the cohesion of the walls of the new vessels is certainly not normal; and the many hæmorrhages which ensue on the slightest provocation are not all brought about by diapedesis but are some of them due to rupture. A most pernicious *circulus vitiosus* now begins; for while fresh exudation is repeatedly escaping from the new vessels, the exuded materials are meanwhile transformed into new vascularised membranes, so that, even when the original cause of the inflammation has long since disappeared, no rest is allowed the affected organ. One might be tempted to ask even, how under these circumstances can such adhesive inflammations ever come to an end, unless indeed the conditions be so favorable that the newly formed vessels and tissues are protected for a time against injurious influences, and so become consolidated and acquire powers of resistance equal to those of the old ones. When this occurs the *circulus vitiosus* is broken, and the entire process terminated. Yet, unlike other terminations of inflammation, the part is not restored to its original condition, for the newly formed tissues are *permanently* present. They take the form of *adhesions, thickenings, indurations, appendages;* their arrangement being determined essentially by the build and anatomical structure of the organ in which the inflammation has been seated. Along the vessels and other canals we have *tubular indurations* (periarteritis, peribronchitis, and also perineuritis); in connective-tissue membranes tendinous *thickening* and *opacity* (arachnitis, endocarditis); around foreign bodies more or less thick connective-tissue capsules; in the serous membranes *adhesions* and *membranous depositions* (pleuritis, pericarditis, peritonitis, arthritis, and pachymeningitis); and lastly in hepatitis, nephritis, orchitis, an *increase of the interstitial connective tissue.* However much these may differ in external habitus, we have in every case to do with one and the same thing, namely, *newly formed vascular connective tissue,* the final product of a chronic inflammation which has generally speaking already run its course. But since the process has, as a rule, terminated, it is not really correct, as you will admit, to still speak of chronic inflammation when describing the above-mentioned conditions, and the names you have just heard would hardly be in use—the adhesions of the pleura would scarcely be termed pleuritis, or the condensed and increased interstitial tissues of a liver or kidney be known as hepatitis or nephritis—did not one circumstance very emphatically point to the progress almost everywhere of a continuous change. This is the property and tendency of the young tissues to shrink, to shorten, to *contract,* after the actual formative process is at an end. With regard to the cause of the contraction, I would not have you, led astray perhaps by the expression employed, suppose that it consists in any remarkable or even enigmatical property or power peculiar to the inflammatory new-formation. The process is rather to be placed in a very extensive category of pathological phenomena, to which the term "*active atrophy*" is commonly applied. Reserving the more thorough discussion of this process for a subsequent occasion, it will now be sufficient to call attention to the rule, *that the organism preserves nothing which it cannot in some way utilise for its purposes;* and on calling to mind how, in inflammatory regeneration and connective-tissue formation, an excess (*i. e.* over the needs) is, as a rule, produced, it will appear but a simple consequence of this rule that a diminution, a disappearance, should subsequently take place. This gradually progressive atrophy involves mainly the newly formed vessels. In pannus vasculosus of the cornea, in the superabundant formation of granulations in wounds, so-called *caro luxurians*, or in other cases where the atrophy is advantageous, the physician is often called upon to further it, and the production of mortification of the vessels by means of nitrate of silver is mostly attended by the best results. Yet such assistance is far from being necessary everywhere. The gradually increasing pallor of the cicatrices, which were at first so intensely red, teaches that, as time passes on, the newly formed vessels undergo atrophy and disappear, even without the aid of the physician's art. The change in the vessels is quickly followed by the atrophy of the new connective tissue surrounding them, as well as of any superfluous portions of the specific tissues originating in true regeneration. In this way redundant layers of epithelium and masses of callus disappear; and the highly vascular adhesions are transformed into *white, tendinous cicatrices.* But in addition to these changes of an advantageous, or at any rate, harmless character, others of much greater moment may result from the process of contraction. It may lead to stenosis of tubular organs, as *e. g.* the blood-vessels, the ducts of glands, the intestines, the air-passages; or compression or flexion may be the result, *e. g.* in connection with the nerves, the uterus, or the Fallopian tubes. Again, the contraction may end in the atrophy and destruction of great portions of parenchymatous organs, as occurs in cirrhosis of the liver and in contracted kidney; in shortening and deformity of the valves of the heart; or in fibrous ankylosis of a joint with resulting malposition of the affected limb, &c. Many more such examples might be given, but the foregoing are sufficient to show that the same chronic form of inflammation, the effects of which are utterly unimportant when a circumscribed pleuritic adhesion or clouding of the meninges is the result, may at times be attended by the most serious consequences to the human organism.

We have now completed our discussion of inflammation. I have attempted to lay before you in detail the peculiarities of the circulatory disturbance on which this process depends; I have enumerated the causes capable of producing the disturbance, so far as they are at present known, and I have, in conclusion, dealt with the subsequent destiny of the inflammatory products. Throughout the entire exposition I have, I believe, clearly distinguished between what has already been added by observation and experiment to the body of thoroughly established scientific fact, and what is still of a hypothetical character. Nor, I think, have I concealed from you how great and palpable are the gaps in many portions of this subject. I need only mention, *e. g.* the inadequacy of our knowledge with regard to the nature of the changes in the vessel walls as well as of the chemical processes taking place in the exudations. But whatever I may have said, it was with the events occurring in connection with the circulation and transudation that I chiefly concerned myself; and the retrogressive, and more especially the regenerative, processes taking place in the tissues and their elements during inflammation should, I considered, be introduced only on practical grounds, because of their nearly constant association with the inflammatory process proper. Inasmuch as we were dealing with the pathology of the circulation I was justified, I think, in confining myself to a discussion of the disturbances connected with the vessels, and in refraining from a consideration of the alterations occurring in the constitution and function of the inflamed organs. In treating of the pathology of tissue-metabolism we shall, in any case, have to return to the subject of the retrogressive changes and the formative processes in the tissues, and not till after we have dealt with the pathology of the kidney, the stomach, in short of each organ individually, can the functional disturbances attending a nephritis, gastritis, &c., be properly explained.

The only subject which might naturally be appended here is a discussion of the consequences resulting to the *circulatory mechanism, i. e.* to the heart and vessels, from inflammations. But ought you need to be reminded how important a part is played by inflammatory processes among the factors detracting from the effective work of the heart? Pericardial effusions and synechia of the pericardium, abscesses, and fibrous indurations of the myocardium, adhesions, and retractions of the cardiac valves,—what are they but the products and terminations of inflammations of all varieties, from the fibrinous to the purulent, on the one hand, and to the productive, on the other? Nor can I add anything to what you already know as to the significance of inflammations for the vessels. It is obvious that the *possession of vasa vasorum* determines whether the vessels, as organs or independent parts, can become the seat of an inflammation. Only in vessels whose calibre is such that their walls are supplied by vasa vasorum can an arteritis or a phlebitis occur. They are then liable to productive or to purulent, to acute or chronic inflammations. It would be difficult to find better examples of chronic productive inflammation than are offered by endo- or peri-arteritis fibrosa, while the purulent phlebitis which sets in as the result of the puriform softening of a thrombus, or in consequence of the extension of a phlegmonous inflammation to the wall of a vein in its proximity, reproduces even to the minutest details the typical characters of an infective purulent inflammation. But you will hardly desire that I should now recur to a subject with which we so thoroughly occupied ourselves only a short time since.

Such being the state of affairs, it may perhaps be more profitable to turn our attention to another aspect of the relations subsisting between the circulatory apparatus and inflammation. If inflammation be simply a peculiar alteration of the vessel walls brought about by some abnormal condition which acts for a certain period on the vessels and excites their reaction, are we not irresistibly compelled to ask whether a considerable deviation of the circulation from the normal may not, or rather must not, become a cause of inflammation? Now, among the causes of inflammation we have made the acquaintance of one local disturbance of the circulation, namely, severe arterial ischæmia of long duration. If a vascular area be for a certain time deprived of arterial blood, a relaxation of the muscular coats, with very considerable dilatation of the vessels, is the result. At the same time the walls are altered in such a way as to oppose an increased frictional resistance to the blood; and the capillaries and veins become much more permeable than before, not only to the liquor sanguinis, but also to the corpuscular elements. All the factors making up an inflammatory disturbance of the circulation are, you will notice, present here; and when you see an ear in this condition, *i. e.* greatly swollen, of a dark red hue, hot, painful, and movable with difficulty, you have not a moment's hesitation in pronouncing it "inflamed." It is true that no similar effect is observable in connection with the other disturbances of the circulation which might here come into consideration, namely, the slighter degrees of anæmia and venous stagnation, even when they persist for a very long time. But in view of the essential differences in the nature of the circulatory disturbance, a like effect is scarcely to be expected, while it is easy to show, on the other hand, that these alterations of the normal circulation may also acquire considerable importance in inflammation. They may, in the first place, exert an influence on the severity of the process, as well as on its *duration* or *course*. In an anæmic organ the great danger attending inflammation is its liability to terminate in gangrene—a result which may be very readily demonstrated on a rabbit's ear by adopting the method of Samuel,* and tying the principal artery of the ear before painting with croton-oil. Precisely analogous experiences are but too commonly met with by the physician in patients with uncompensated or imperfectly compensated cardiac lesions; where any inflammation that may set in is characterised by its tediousness and severity. They may, in the second place, act by causing inflammation to be set up by noxæ so slight that were the circulation healthy no reaction whatever would take place; the most striking examples of this are afforded by the so-called *hypostatic* inflammations. From these facts but one inference can be drawn, that the vessel wall has been reduced by the antecedent circulatory disturbance to a condition of what may be called *unstable equilibrium*, from which it is only a step to the actual inflammatory alteration.

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* Samuel, 'Virch. A.,' xl, p. 213, xliii, p. 552, li, pp. 41, 178, lv, p. 380. 'Der Entzündungsprocess,' Leipzig, 1873.

But not merely must the *circulation* be normal if the vessels are to maintain their condition unimpaired; the *blood* itself must be *normally constituted*. Hence you will not be surprised to learn that results very similar to those occurring in individuals with local disturbance of the circulation are found in persons whose blood has undergone important changes of composition. I formerly pointed out (p. 338) the tendency of all inflammations in *hydræmic* and *diabetic* subjects to run a severe course and to terminate in gangrene. Moreover, the second point of similarity between the two classes of cases, namely, the great proneness to inflammations, is so considerable, especially in hydræmic individuals, that hydræmia may fairly be regarded as a *predisposing cause*.

Although under the circumstances just mentioned this predisposition is quite intelligible, we are as yet unable to state the causes of that peculiar readiness and frequency with which many individuals acquire this or that inflammation under the influence of particular noxæ—noxæ which perhaps produce no effect whatever on others. At present we have no alternative but to assume the existence of a certain *feebleness* of constitution in the vessel walls, as the result of which they possess less capacity for resistance than is normal. This feebleness or incapacity for resistance may be acquired, but there is no doubt that it may also be *congenital*. Since, at least, we meet with persons who from childhood are attacked on every slight provocation by a catarrh of some one of the mucous membranes, it appears but a step to the assumption that the vessels of these membranes are specially *susceptible of irritation and injury* and are *deficient in resisting power*. And such an hypothesis meets, it is obvious, with satisfactory confirmation in the fact that certain inflammations, or rather, inflammations of certain organs, are *hereditary in many families*. It is not the inflammation itself, but the *predisposition* to inflammation depending on the constitution of the vessels that is here transmitted; and you will therefore carefully distinguish between these cases and the direct *inheritance of an inflammation.* Inflammation may be inherited, but only when it belongs to the *infective* class. When the child of a syphilitic father comes into the world with a gummatous periostitis or hepatitis he has inherited, not the predisposition, but the *specific infective inflammation* itself; in other words, the *cause of the inflammation* is also transmitted from the father to the child. The manner in which this result is brought about is capable of being explained from our present theoretic standpoint. Two alternatives present themselves; the first that the virus in question *is already intermingled with the generative products of the parents,* with the semen or the ovum, and is accordingly incorporated with the embryo from the first. So far as I see, we are *compelled* to accept this hypothesis where, for example, the child of a syphilitic father is born with the disease while the mother has remained free from all symptoms of syphilis both before and during the pregnancy. Moreover, in favour of this assumption, which many may think mysterious or at least very rash, there is a very complete analogy, and a gross one to boot, in the well-known *pébrine* or "*spotted disease*" *of silk-worms,** a disease which proves so destructive to the entire brood because the eggs and the semen of the affected individuals also contains the germs. There is, however, another means whereby the "inheritance" of infective inflammations and of infective diseases in general may take place, namely, by *infection through the medium of the placenta.* For to deny the possibility that the parasitic virus contained in the placenta may pass from the circulation of the mother into that of the child, on the ground that particles of vermilion, which have been introduced into the blood of the pregnant rabbit, cannot be discovered in the vessels or tissues of the fœtus, presupposes such an amount of *naïveté* as almost to make its possessor an object of envy. On the contrary, we are at present acquainted with a series of facts which are calculated to completely divest this possibility of its hypothetical character. It has over and over been observed that the children of mothers who have passed through an attack of *variola* during pregnancy have been born with pustules or their cicatrices;[*] and perhaps still more convincing is the fact, testified to by many observers, that the *spirillum of relapsing fever* is discoverable in the blood of the fœtus when the mother has fallen ill of this disease during pregnancy.[†] Moreover, the transmission of measles and of scarlet fever from the mother to the fœtus is reported by a few authors.[‡] A short time ago there occurred in our institute here the case of a child a few days old, in whom the autopsy revealed an exquisite *synovitis* involving many of the joints, which contained a cloudy fluid rich in pus-corpuscles. No abscess or injury was anywhere present, but the mother had been for several weeks previously prostrated by a severe rheumatic fever. Who would undertake to decide, on the facts of this case, that an intra-uterine infection with the virus of acute rheumatism had not here taken place? Whether infection through the medium of the placenta occurs in syphilis is still a moot point with syphilologists; *a priori* I see nothing against it.

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* On the subject of pébrine cf. the numerous papers by Pasteur in the 60th vol. of the 'Compt. rend.;' Frey und Lébert, 'Vierteljahrsschrift d. naturforsch. Ges. in Zürich,' 1856; Bassi, 'La Pebrina, Malattia del Baco da Seta,' Milano, 1868; Haberlandt u. Verson, 'Studien über d. Körperchen d. Cornalia,' Wien, 1870.

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[*] Cf. L. Meyer, 'Virch. A.,' lxxix, p. 43.

[†] Spitz, 'Die Recurrensepidemie in Breslau im Jahre 1879,' I.-D. Breslau, 1879; Albrecht, 'Petersb. med. Wochenschr.,' 1880, No. 18.

[‡] Cf. Runge, 'Volkmann'sche Vorträge,' No. 174.

CHAPTER VI.

HÆMORRHAGE.

Nomenclature.—Hæmorrhage by rhexis and by diapedesis.—Their differential diagnosis.

Causes of rupture of the vessels.—Wounds.—Erosion.—Predisposing causes of the so-called spontaneous ruptures.—The ecchymoses found in persons dead of asphyxia.—Menstruation.—Hæmorrhages in poisoning with phosphorus and other substances.—The hæmorrhages of infective diseases.—The vessel walls affected by the constitution of the blood.—Scurvy.—Hæmophilia.—The newly formed vessels easily ruptured.—Cohesion and porousness of the vessel walls.

Death from hæmorrhage.—Spontaneous arrest of hæmorrhage by thrombosis.—Healing of vascular ruptures.

Subsequent history of the effused blood.—Coagulation.—Resorption of the fluid constituents.—Hæmatoidin.—Cells containing blood-corpuscles.—Formation of pigment.

Secondary inflammation.—Organisation of the extravasation.—Apoplectic cysts and cicatrices.—Dissecting inflammation.

Significance of hæmorrhage for the implicated organs.

OF the pathological changes in the vessel walls which must ecessarily influence the circulation, the *interruption of their ontinuity* still remains to be discussed. The effect of such nterruption may be expressed in few words. When a defect, gap, is produced at any point in the vascular system all esistance ceases there; and the blood will in consequence ow towards it and *escape through the aperture*, with an energy hich naturally is greater the higher the pressure prevailing in the part of the vascular system involved; *bleeding, hæmorrhage* occurs. Inasmuch as an interruption of continuity may take place at any point in the circulatory apparatus, the bleeding may proceed from the *heart*, or the hæmorrhage be *arterial, venous*, or *capillary*. We recognise in addition a *parenchymatous* form, where the blood escapes from arteries, veins, and capillaries together. Moreover, these hæmorrhages are differently named according as the quantity of blood escaping from its natural reservoir is greater or less. The smallest of all, which are at most not larger than a pin's head, are called *punctiform* hæmorrhages, *ecchymoses* or *petechiæ*; when the bleeding is somewhat larger the term *suffusion* is employed. If the meshes and interstices of a part are filled to distension with blood as the result of hæmorrhage, there being at the same time no tearing or breaking down of the tissues, the condition is called a *hæmorrhagic infarct*. When, on the other hand, the tissues of the part are disintegrated we speak of a *hæmorrhagic* or *apoplectic focus*; and if the bleeding is so copious that the effused blood forms an actual tumour, of a *hæmatoma* or *bloody tumour*. All these are hæmorrhages into the tissues surrounding the vessels, or so-called *internal* hæmorrhages; contrasting with which are the forms termed *external*, where blood is effused directly outwards or into cavities lying very near the exterior of the body and communicating freely with it, *e. g.* the cavities of the mouth and nose or the vagina. Intermediate between these are the hæmorrhages into cavities far removed from the surface of the body, as *e. g.* the stomach or small bronchi; or into cavities having no outward communication, like the serous sacs; yet these varieties are also commonly termed *internal*.

I need hardly describe the appearance of an extravasation, for indeed I know nothing with which it could be confounded. Yet, on meeting with an aggregation of blood-corpuscles outside the vessels, it would be rash to assume at once that a vessel must be ruptured there, and *hæmorrhage by rhexis* have occurred. The experience we have already had concerning the diapedesis of the red blood-corpuscles forbids us to do so. In two entirely different conditions, we found that a passage of red blood-corpuscles through the unruptured vessel wall takes place; in one as a consequence of *mechanical hyperæmia*, and in the other during the course of certain processes, having an alteration and disorganisation of the vessel walls as their common characteristic, *i. e. hæmorrhagic infarction* and *inflammation*. We were able to connect the diapedesis in mechanical hyperæmia with the abnormal rise of pressure in the interior of the capillaries and veins, while the inflammatory diapedesis, as we shall briefly designate the second form, was, on the contrary, quite independent of the internal pressure, and took place from the same vessels just as readily under normal as under increased pressure, and more especially under diminished pressure also. Having already exhaustively treated the processes under discussion, I need not now show that in both cases the blood-corpuscles really leave the vessels by passing through the uninterrupted vessel wall, and not through minute apertures in it. Call to mind how on the removal of the impediment from the vein the normal blood-stream was instantaneously established, without the passage subsequently of even a single blood-corpuscle through the supposed apertures. Remember, too, that in inflammation the blood-stream proceeded without intermission in the capillaries from which at the same time red blood-corpuscles were extravasating, no current setting in towards the apparent opening, as is always, and must necessarily be, the case where an actual defect exists. Moreover, we possess an extremely accurate criterion for determining whether an unbroken or a defective endothelium is present. For wherever the endothelium receives the least injury one or more colourless corpuscles at once become adherent, and are eventually transformed into a coating of fibrin; yet we see nothing of this kind in the vessels through which red corpuscles had previously extravasated, either after the removal of an obstruction from a vein, or during the course of, or following, an inflammation. But we can dispense with such proofs. For we know that it is not blood which passes out of the vessels under these circumstances—at least, if we understand by blood a fluid such as circulates in the interior of the vascular system, *i. e.* a watery solution of certain albuminous substances and salts of a definite concentration, in which are suspended red and colourless corpuscles in certain numerical proportions. However large the quantity of red corpuscles contained in the transudation of mechanical hyperæmia, the latter is always poor in albumen and fibrin; and the exudation in inflammation, even when of the hæmorrhagic form, is a fluid bearing no resemblance to blood. If, then, by hæmorrhage we understand an effusion of *genuine blood*, *i. e.* of blood containing all its constituents in their proper proportions—which is undoubtedly a legitimate definition—it cannot possibly occur except through interruption of the continuity of the vessel wall, *i. e.* by *rhexis*. But on reflecting that when blood escapes from the vessels it at once mixes with the fluids contained in the cavity or parenchyma, and above all, on considering what the constituents of the blood are, you will quickly come to the conclusion that it is only and solely the blood-corpuscles that can be relied on in diagnosing a hæmorrhage. Now when you meet with a hæmatoma, a patch of hæmorrhage, or even a suffusion, you will of course have no more doubt that the rupture of a vessel must have taken place than you would on seeing a sudden rush of blood from the mouth and nose of an individual; and a mass of coagulated blood contained in the stomach, or in a cavity in the lung, will certainly induce you to look for an opening in one of the larger vessels. Yet the matter is far from being always so simple. An ecchymosis due to the rupture of a capillary is quite as small as the accumulations of red blood-corpuscles which in inflammation, or in a rabbit's ear after being deprived for a considerable time of its arterial blood-supply, are visible to the naked eye in the shape of punctiform or linear hæmorrhages. Moreover, should the diapedesis continue for a longer period, as occurs in hæmorrhagic infarction on occlusion of a terminal artery, or in protracted venous hyperæmia, the extravasated blood-corpuscles may accumulate to such an extent as to equal those of a large-sized circumscribed hæmorrhage in number. Nor can a definite conclusion always be drawn from the form and figure of an extravasation any more than from its amount. A markedly hæmorrhagic ascites may equally well be due to a plentiful admixture of emigrated blood-corpuscles with the transudation or to the rupture of a vessel; and the true hæmorrhagic infarct presents precisely the same appearance as a parenchymatous hæmorrhage of the affected part. In many cases where a naked-eye inspection is of no avail, a decision may be arrived at microscopically, if the part in question can be examined very shortly after the bleeding has taken place. For it may be confidently asserted that in hæmorrhage by diapedesis there will be found, in addition to the punctiform ecchymoses or more extensive aggregations, capillaries in some of the patches surrounded by blood-corpuscles, while other cells may perhaps be detected in the act of passing through the walls—which does not, of course, occur in hæmorrhage by rhexis. Yet we shall not often be in a position, especially in the case of human beings, to carry out immediately after the bleeding such an accurate microscopic examination of the finest blood-vessels, completely preserving at the same time the mutual relations of the parts, and hence there arises the necessity of attending before all things to the known *etiology* of vascular ruptures. The causes of the diapedesis of the blood-corpuscles having been previously discussed, let us now see what is known of the causes of rupture of the vessels.

Perfectly healthy vessels may be ruptured by *external* agencies of the most varied kinds. Of these I may instance wounds of all sorts, fractures of bone, bruises and severe contusions, to which *e. g.* the cephalhæmatoma and othæmatoma are due; the tearing of mucous membranes by solid bodies, as catheters and urinary calculi; the bites of animals, including those inflicted by intestinal worms, *e. g.* by *Anchylostoma duodenale*, &c. In the second place, it is not uncommon for vessels to be eroded from without by ulcerative processes, as occurs in round ulcers of the stomach, in cancerous, tuberculous, or other malignant ulcerations, as well as where vessels are situated in the midst of gangrenous regions. Yet it hardly ever happens in these cases that the vessels continue perfectly intact up to the moment of rupture; the ulcerative or necrotic process is wont to extend itself to the vessel walls, and it is the already diseased portions of the latter which give way and are perforated. Such hæmorrhages would indeed occur much more frequently than they do were it not that very commonly the blood in the vessels whose walls become involved in the processes of mortification and ulceration, forthwith coagulates. While, then, in these cases the vessels are mostly diseased when the rupture occurs, this applies with still greater force to the vast majority of all so-called *spontaneous* hæmorrhages, or hæmorrhages not dependent on external influences. To this class all the more severe structural changes of the heart and vessels supply their contingent, more especially those which lead to a thinning of the walls; undoubted examples of such are softening of the myocardium, atheromatous degeneration of arteries, and in particular *aneurysms* and *varices*. The aneurysms most predisposed to rupture are the so-called *aneurysmata spuria* (in which only some of the coats go to form the wall of the sac), as well as those which have arisen from injury to the vessel wall, whether external or internal, as *e. g.* through hard, pointed emboli.* Yet, as you are aware, the tendency of pathological anatomy has of late been to abandon the sharp distinction formerly drawn between *aneurysma verum* and *spurium*, since minute examination has shown that a defect of one or other of the coats, especially of the *t. media*, is something very common in the wall of the true aneurysms also. The view that the vessel wall suffers a loss of cohesion as the result of fatty degeneration is extremely common among physicians. With regard to the heart, it can hardly be denied that a high degree of fatty degeneration of the myocardium lowers its powers of resistance; but that this also applies to the vessels is not so certainly established. True, the coexistence of hæmorrhages and fatty degeneration of the vessels has often been determined, and is especially frequent *in acute phosphorus poisoning*,† yet it is far from settled that these hæmorrhages have actually taken place by rhexis. Fat-droplets, in larger or smaller groups and aggregations, are met with so very frequently in the intima and adventitia, and even in the media of arteries, without the slightest bleeding, that I at least have again and again been compelled to doubt whether the vessel walls really become more disposed to rupture in consequence of fatty degeneration. The possibility of such a result I am willing to admit:

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* Ponfick, 'Virch. A.,' lviii, p. [illegible]

† Klebs, 'Virch. A.,' xxxiii. [illegible] A.' lv, p [illegible]
Heschl, 'Wien. med. W[illegible]

[illegible] caused by one [illegible] slight trauma [illegible] than not [illegible] vessels being [illegible] Hence [illegible] called [illegible] in fact [illegible] [illegible] the like, [illegible] the rupture [illegible] ages have been [illegible] instances of spontaneous blood [illegible] of the lungs, have lately [illegible] on the condition [illegible] almost all seem to the [illegible] portions of the arterial wall [illegible] diseased. Even in [illegible] copious hæmoptysis [illegible] when the patient succumbs to the hæmor[illegible] and the lungs may therefore be examined immediately [illegible] the occurrence, we are often able to demonstrate [illegible] ed aneurysm of one of the branches of the pulmonary [illegible] which, as a rule, runs naked through a cavity [illegible] the bleeding does not proceed from a [illegible] l dilatation, the vessel wall has always been [illegible] ed and rendered friable by becoming [illegible]

Fraentzel, [illegible] 'Charité-Annalen,' [illegible]
[illegible] 'Virch. A.,' xxxi. [illegible]

phthisical ulcerative process. I need hardly say that where such predisposing causes are present, rupture is essentially favoured by a rise of blood-pressure, either general, in whatever portion, arterial or venous, of the circulation is involved, or merely local. Hence it is that among cases of cerebral hæmorrhage such a considerable percentage of hypertrophies of the left ventricle is met with, and that such copious hæmorrhoidal bleeding takes place in mitral stenosis. But that a hypertrophy, even when very considerable, or a congestion can ever of itself be sufficient to cause rupture of a vessel previously intact, I hold, as already stated (p. 142) to be extremely improbable. Volkmann* has shown that the carotid of a dog does not rupture when subjected to an increase of internal pressure *fourteen times* greater than the natural; and not till he had raised the tension in the v. jugularis to *one hundred times* the normal did this vessel burst. Facts such as these make it more than questionable whether in the case also of the smaller arteries and veins the blood-pressure ever reaches such an elevation as to burst their walls. Indeed, a rupture even of capillaries from this cause will appear to you doubtful, on calling to mind what an enormous rise of pressure is occasioned in them by entirely cutting off the escape of blood by the veins, and that this is never attended by laceration of capillaries, but only by a copious diapedesis of red blood-corpuscles. In support of the view that very intense congestions may result in laceration of the capillaries, it is usual to refer to those hæmorrhages which set in during dry-cupping—not constantly, it is true, but still in many instances; and which also attack some persons on exposure to a very rarefied atmosphere. Nevertheless the result is attributable rather to the rapid dessication which the superficially placed mucous membrane of the lips, conjunctivæ, and nose undergo in the attenuated atmosphere, and to the resulting rhagades, than to the supposed rise of blood-pressure. Further, on a former occasion (p. 143), I dwelt on the entire want of similarity between the circulatory disturbance following the application of dry cups and arterial congestion. How little calculated the latter is *per se* to lead to rupture of the capillaries is most clearly shown whenever a curarised animal is asphyxiated or poisoned by strychnine. Not only does an enormous rise of the arterial blood-pressure take place here, but, as was proved by Heidenhain,* the cutaneous arteries dilate, so that their capillaries are subject to an internal pressure more excessive than could ever be occasioned by congestion; and yet not one of them ruptures. Accordingly, the healthy capillaries, at least of the skin, are capable of offering adequate resistance to the most extreme elevations of pressure, even when these originate suddenly. This, it is true, refers only to curarised animals, yet it obviously follows therefrom that when, in dogs and rabbits which have not been paralysed, ecchymoses similar to those occurring in asphyxiated human beings are observed as the result of asphyxia and strychnine poisoning, their cause must be sought for in some factor other than the rise of blood-pressure. As a matter of fact, the truly classical ecchymoses of asphyxia, those met with in the pleuræ, lungs, pericardium, or elsewhere in the thorax of persons who have died asphyxiated, are nothing but the effects of the stronger *drawing or sucking action of the thorax while the entrance of air into the lung is obstructed;* the thorax, enormously distended by the forced inspirations, and cut off from all communication with the atmosphere, acts like a large and most powerful *cupping-glass.* But should petechiæ be found in other parts of the bodies of persons dying from asphyxia or tetanus, they may more rationally be referred to the mechanical factor, the eclampsia, than to the rise of blood-pressure; and with this view the common occurrence of capillary ruptures in hooping-cough and in general convulsions, *e.g.* of the epileptic, is quite agreeable. In these cases we have to do with small muscular hæmorrhages, or possibly in addition with ecchymoses of delicate and lax tissues, such as the brain, conjunctiva, sub-pleural or sub-pericardial tissue; while should they under such circumstances make their appearance elsewhere—in the skin,† for example—you may be perfectly certain that you are then dealing with persons whose vessels are diseased and for some cause or other more easily lacerable.

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* Volkmann, 'Haemodynamik,' p. 290.

With the assistance of the facts now mentioned, you will be able in very many cases to satisfy yourselves whether an extravasation met with anywhere is due to a true *hæmorrhagia per rhexin*, or whether a diapedesis is at the bottom of it. But there remains an entire series of hæmorrhages, *which cannot be referred either to one of the known causes of vascular rupture or to diapedesis.* Are we not, strange as it may appear, still ignorant of the manner in which the physiological *hæmorrhage of menstruation* is brought about? So far as the effusion into the follicles is concerned, it cannot reasonably be doubted that it depends on an actual laceration of the vessels, for in fresh cases there is not the least difficulty in demonstrating the rent in the capsule. In the uterine mucous membrane, on the other hand, rupture of the vessels has not up to the present been observed; and even if it takes place, its demonstration must be a matter of considerable difficulty, inasmuch as the ruptures can hardly be other than capillary. From another point of view, the menstrual hæmorrhage, being of a lasting character, and yet furnishing but a relatively small amount of blood, could very well be interpreted as a diapedesis. Here then the modus of the bleeding is still involved in obscurity; and the same is true of the hæmorrhages setting in in the course of many acute diseases. Such are observed, in the first place, in a number of cases of marked poisoning with substances whose chemical characters have in other respects hardly anything in common. In Schmiedeberg's[*] laboratory this connection has been made out, for example, in acute poisoning with platinum and antimony, and still more markedly in acute and chronic mercurial poisoning. In these cases it is in the intestinal canal that the hæmorrhages are principally seated, although other regions are not exempt. True, whether the cause of the hæmorrhages, assumed to be in operation by the writers referred to, namely the considerable fall in blood-pressure, be really the correct one is probably more than doubtful. The fall in blood-pressure is very far from adequately explaining the widely distributed and often copious hæmorrhages which make their appearance in acute phosphorus poisoning, by predilection in the adipose tissue, and then in the peri-

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* Ostroumoff, 'Pflüg. A.,' xii, p. 219.

† Cf. Traube, 'Gesammelte Beiträge,' iii, p. 461.

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[*] Kebler, 'Arch. f. exper. Pathol.,' ix, p. 137; Soloweitschik, ibid., xii, p. 438; v. Mering, ibid., xiii, p. 86.

and endocardium; in the liver and kidneys, in the pelvis of the kidney and bladder; in the brain and its membranes; in the lungs, stomach, and intestinal canal; in short in all possible organs. Resembling phosphorus poisoning in this and in many other respects are two highly interesting diseases, which, however, differ very widely from it in point of etiology: they are *acute atrophy of the liver* and the severe form of mechanical icterus, the so-called *icterus gravis*. *Putrid intoxication* may also be included under this category. For on injecting putrid fluids into the circulation in dogs, there is very quickly developed a tendency to small or larger effusions of blood in the stomach, intestinal canal, mesentery, pleuræ, kidneys, and various other regions.* And in men too, in analogous circumstances, *i. e.* when putrid material has gained entrance into the juices of the body, all sorts of ecchymoses, small and large, are of very common occurrence. But despite the frequency of such hæmorrhages, we are, as was stated, still ignorant whether they take place from ruptured or from uninjured vessels.

Further, there are a number of typical *infective diseases* which are distinguished by what has been appropriately called a *hæmorrhagic diathesis*. The hæmorrhages often proceed exclusively from the capillaries, as in *petechial typhus* and *endocarditis ulcerosa*. Yet they may acquire very considerable dimensions in some of these diseases, as *yellow fever* and *hæmorrhagic smallpox*. It often happens that every infective disease accompanied by abundant hæmorrhages, which cannot be referred to any other sharply characterised type, is regarded as an example of the latter of these affections, although it is certain that very different maladies may here be in question. Occasionally we find a marked hæmorrhagic diathesis associated with other *severe infective diseases*, *e. g.* *typhoid fever* and *congenital syphilis*.† Since in all these cases we have to do with diseases due to infection, we can not doubt that parasitic organisms are present in the interior of the body, *i. e.* in the blood-vessels, even where they have not as yet been so positively demonstrated as in ulcerative endocarditis and typhoid ; yet this does not throw much light on the origin of the hæmorrhages. It is possible, indeed, that the bacteria circulating in the blood exert a direct pernicious influence on the vessel walls ; and such an assumption obviously suggests itself where, as in ulcerative endocarditis and many septic processes, a capillary has been repeatedly discovered plugged by a colony of micrococci and occupying the centre of an ecchymosis of the skin, kidney, or pia mater.* But even granting that it is the action of the colony of bacteria on the affected portion of the capillary wall that produces the hæmorrhage, the finer mechanism on which the bleeding depends is still unknown to us. If, as will appear very probable from other facts to be discussed later on, the direct action of the bacteria on the capillary wall is to produce necrosis, it would be, as you will readily understand, equally open to suppose either that the wall becomes more permeable to the red corpuscles during the gradual development of the necrosis, or that one or more minute portions of it give way owing to the diminished cohesion. In addition, I wish to lay special emphasis on the fact that the attempt to discover a colony of micrococci in the midst of a punctiform hæmorrhage is by no means invariably successful, even in ulcerative endocarditis ; while, in all the remaining diseases, the demonstration of such a mechanical factor is at present quite out of the question. Hence, a second possibility must certainly be kept in view, namely, that *the blood is so damaged and deteriorated in composition* by the organisms circulating within the vessels as to produce *indirectly* a profound lesion of the vessel walls. For although the influence which is exerted on the circulation by changes in the constitution of the blood still remains to be discussed in succeeding lectures, I have already so frequently drawn attention to the reciprocity of action between blood and vessels that the idea will appear quite plausible to you ; and you will have no difficulty in admitting that the condition of the vessel walls must suffer severely as the result of any grave deterioration in the composition of the blood. Nor is there any difficulty in adducing definite facts from pathology to show that the vessels react by hæmorrhage when the blood becomes impaired in quality. I have now in mind—leaving the poisons just mentioned out of consideration—all severe and lasting *anæmias* whatever their origin; in these, small or larger ecchymoses are among the most constant symptoms. *Leukæmia* also very often brings hæmorrhages in its train. But it is pre-eminently *scurvy* that is wont to be cited in proof that an impairment of the composition of the blood can call forth copious hæmorrhages. The nature of the defect in scorbutic blood, the deviation from the normal, on which the tendency to hæmorrhage depends, is, it is true, at present quite unknown to us. All attempts at solving the problem experimentally have so far utterly failed; and how little the analysis of observed cases has contributed to its elucidation is best shown by the fact that the responsibility is thrown on the presence of an excess of salts in the food by some authors of good repute, and on precisely the deficiency in saline matters by others no less reputable. It is certain, at any rate, that scurvy is most prone to attack ill-nourished individuals and such as are unfavorably situated as regards their dwellings, &c. Yet in this respect no essential difference is presented by many other diseases of epidemic occurrence, *e. g.* typhus; and in any case this circumstance alone does not exclude the possibility that other and much more specific factors may co-operate in the production of scurvy. Indeed many unprejudiced physicians have been impressed with the notion that scurvy is a miasmatic-contagious infective disease;* and Klebs, in a recent though very brief communication,† reports the finding in the blood of scorbutic persons of large numbers of most minute organisms, which belong rather to the infusoria than to the bacteria, and are called by him *Cercomonas globulus* and *C. navicula*. Should it turn out that such organisms are constantly present in the blood of scorbutic persons, the question would of course arise—is not the deterioration in its composition chiefly brought about by them? Possibly they may produce this effect by destroying the structural elements of the blood, and especially the red-corpuscles; for if we ask ourselves whether there exists any factor common to all the cases of hæmorrhagic diathesis just discussed, I should be at a loss to mention any, except it be *the deficiency of functionally capable red blood-corpuscles.* This feature at least is equally characteristic of poisoning by metals, the forms of anæmia, and, as you will learn later, of icterus gravis. The experience that local ischæmia is sooner or later invariably attended by hæmorrhages may fairly be utilised in support of the existence of such a connection; and the hæmorrhages of acute phosphorus poisoning will also appear more comprehensible from this point of view, on learning that here in all probability the red corpuscles suffer an extreme and rapid decrease in numbers, and that, in any case, their power of absorbing oxygen is very seriously impaired by the phosphorus. At all events the hypothesis of a connection, or, it may be, a direct dependence, between this tendency to hæmorrhage and the poverty of the blood in functionally capable red corpuscles, is calculated to help us to understand how it happens that the hæmorrhagic diathesis should be met with so frequently, and under conditions apparently so diverse.

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* Gaspard, Magendie's 'Journ. d. physiol.,' ii, p. 1, iv, p. 1; Stich, 'Aus d. Charité-Annalen,' iii, Berlin, 1852, p. 192; Virchow, 'Ges. Abhdlg.,' p. 659; 'Handb. d. sp. path.,' i, p. 242; Panum, 'Virch. A.,' xxv, p. 441, lx, p. 301; Bergmann, 'Das putride Gift u. d. putride Intoxication,' i. Heft i. Dorpat, 1868; 'D. Zeitschr. f. Chir.,' i, p. 373.

† G. Behrend, 'D. Zeitschr. f. pract. Med.,' 1877, No. [illegible] Wachsmuth, 'Ueber Blutungen d. Neugeborenen,' [illegible]

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* On an investigation by Prussak, 'Wien. akad. Stgsb.,' Bd. lvi, Abth. 2, Juni, 1867, cf. Cohnheim, 'Embol. Processe,' Berlin, 1872, p. 36.

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* Cf. Kühn, 'D. A. f. klin. Med.,' xxv. p. 115.

† Klebs, Artikel "Flagellata," in Eulenburg's 'Realencyklopädie.'

But even if this assumption were much less hypothetical than is in reality the case, it could not assist us in arriving at a conclusion as to whether the hæmorrhages resulting from the deterioration in the blood take place *per rhexin* or *per diapedesin*; in other words, whether the profound change in the constitution of the blood, however originating, renders the vessel walls more *permeable* or more *brittle, lacerable.* In frogs which have passed a long time in confinement, it is very common for punctiform and linear hæmorrhages to appear spontaneously (*i. e.* without any recognisable external cause), in the skin, mucous membranes, muscles, &c.; and accordingly we are justified in calling these hæmorrhages *scorbutic.* It has been my repeated good fortune to observe such hæmorrhages *in flagranti* under the microscope, and without desiring to decide as to the co-operation of any kind of bacteria, I have been able to satisfy myself beyond all doubt that the hæmorrhages took place through the unbroken vessel wall. This does not of course prove that the bleeding occurring in men who are the subjects of scurvy or a similar disease takes place *per diapedesin*, especially as the rapidity with which the often very considerable hæmorrhages occur in these diseases lends greater probability to the view that actual rupture of the vessels is the cause. To conclude, it is not, indeed, impossible that in scurvy both the permeability and fragility of the vessel walls are abnormally increased.

As to whether some alteration in the constitution of the blood occurs in *morbus maculosus Werlhofii* also, we are still ignorant. Inasmuch as the genesis of this disease may occasionally be traced back to very early childhood, it appears rather to have a certain relation to the much discussed hæmorrhagic diathesis or *hæmophilia*. Here there is a congenital anomaly of constitution, hereditary in some families, and characterised by the occurrence of hæmorrhage on the very slightest external violence, or even spontaneously; besides which the hæmorrhage when it sets in is usually very violent and profuse. The latter circumstance points, it is true, to the existence in hæmophilia of an abnormally feeble power of coagulation, depending on some cause or other at present altogether unknown. Yet that this disease mainly depends on an abnormal lacerability of the vessel walls is, in the first place, probable *a priori;* and in the second, it has been positively determined by trustworthy observers[*] that at least the larger vessels are actually more easily torn. Thinness of the walls and feeble powers of resistance characterise, we are justified in believing, the entire vascular system in this diathesis; while the limitation of the ruptures to circumscribed spots is easily explainable on the supposition that only those vessels burst which either meet with an injury, it may be a trifling one, or are exposed to a somewhat considerable rise of pressure through congestion or the like. On the other hand, the observations repeatedly made as to the habitual occurrence in certain individuals of hæmorrhage from the nose indicate that the abnormal lacerability may occasionally be confined to isolated vascular areas; and the inherited disposition to cerebral hæmorrhage,[†] often noticed through

[*] Blagden, 'Med. chirurg. Transact.,' viii, p. 224; Schliemann (Schönlein), 'De dispositione ad. hæmorrh. pernic. heredit.,' I.-D. Würzburg, 1831; Virchow, 'D. Klinik,' 1856, No. 23.

[†] Dieulafoy, 'Gaz. hebdom.,' 1876, No. 38.

several generations, also favours this idea. The essential element in all these cases is the congenital nature of the incapacity for resistance, so much so that, as is well known, hæmophilia may sometimes be met with in new-born children. A certain amount of caution must be observed here, and you will not hastily diagnose hæmophilia when in the new born you find multiple hæmorrhages of non-traumatic origin. For, without taking the cases of syphilis hæmorrhagica neonatorum into account, hæmorrhage in the newborn has repeatedly been observed by Klebs* in Prague and by Weigert in our institute. Bacterial infection and embolism were shown by them to be the causes of the extravasation, and accordingly the assumption of a predisposition to hæmorrhage was, to say the least, superfluous.

While the physiological vascular system in some individuals is, accordingly, from the first predisposed to rupture, and in others acquires this tendency under the action of certain agencies, a defective resisting power is, as I have more than once pointed out, the rule in *newly formed* vessels which have developed as the result of pathological processes. This element plays an important rôle, not only in the *vessels of productive inflammation*, but also, in a still higher degree, in those of tumours, especially when growing rapidly. For, here, where a rapid formation of vessels necessarily takes place, one of the most common and dangerous symptoms is hæmorrhage, either in the interior of the tumour or, if the latter borders on a free surface, in an outward direction. For very slight violence or a moderate degree of congestion or hyperæmia is sufficient to rupture the extremely thin-walled and brittle vessels of a cancer of the stomach or of a uterine polypus.

You perceive that in this domain also there is plenty of scope for investigation. We cannot arrive at perfect clearness as long, more especially, as we are unable to answer the first question, whether in any given case we are dealing with a hæmorrhage *per rhexin* or *per diapedesin ;* for the problem cannot be properly put till this point has been determined. Hence it is to be regretted, you will admit, that an examination of the fully formed extravasation so seldom leads to the desired end. When you find in some one of the tissues a single, or several minute extravasations, which are no longer quite recent, by what means will you decide whether one or more vessels have ruptured, or whether a diapedesis has taken place? Perhaps by the relative proportions of the red and white corpuscles in the extravasation? But, just as in diapedesis from the capillaries, so too from a laceration or aperture in the vessel wall, a very much larger number of red corpuscles escape, owing to their greater weight and more rapid removal; and when you consider further how the colourless corpuscles can change their situation, and even disappear by disintegration, that criterion will appear to you worthless. Or will you decide from the occurrence or non-occurrence of *coagulation?* But this itself is intimately connected with the history of the colourless blood-corpuscles in the extravasation, and we are therefore by no means warranted in assuming that the extravasation brought about by diapedesis cannot also coagulate: the hæmorrhagic exudations are very commonly at the same time fibrinous. Yet the processes of hæmorrhage per rhexin and per diapedesin are, despite the harmony of their results, absolutely different; and it is not, as has been said,* mere hair-splitting, to distinguish sharply between them. Anyone who has once observed under the microscope a bleeding following rupture of a capillary, or injury of a larger vessel, will certainly be no longer disposed to regard it as the equivalent of diapedesis. Let no one here speak of possible differences between cold- and warm-blooded animals, between frogs and mammals! If you produce complete ischæmia of the intestines and mesentery of a dog by compressing the a. mesenterica superior, and then after a couple of hours or so remove the clamp, you can see the intestine and mesentery, previously drawn out of the abdomen, becoming covered after a few minutes with punctiform and linear ecchymoses, which continue to enlarge for a time. No unprejudiced person witnessing this will at first have any doubt that a multitude of minute vessels have here been ruptured by the pressure of the returning blood. On cautiously bringing the mesentery under the microscope, however, you at once perceive that everywhere in the midst of the extravasations the *capillary stream continues without interruption,*

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* Klebs, 'Aerztl. Correspdz.-Bl. f. Böhmen,' 1874, No. 21.

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* Böttcher, 'Virch. A.,' lxii, p. 579.

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and this in the identical capillaries from which, as inspection clearly teaches, fresh blood-corpuscles are still passing out. On the other hand make a wound, however minute, of one of the fine vessels—that is to say if, as the result of your manipulation, some one or more of the capillaries be not already torn—and a spectacle of quite another kind is presented to your view. For from all directions, both from the proximal and peripheral sides of the opening, the blood-corpuscles flow as through a funnel towards the aperture; and this continues till some of the colourless cells come to lie in front of it, upon which the blood-stream again flows regularly by. The quantity which has meanwhile escaped need not be more than would extravasate from vessels of equal size with uninterrupted stream. For they are two utterly different qualities of the vessel walls that suffer in the two cases. By the trauma *internal cohesion* is overcome; by the antecedent ischæmia and the exposure the *porosity* or *permeability* is essentially altered. A more or less large amount of cohesion is, of course, a property of all vessels, while, so far as we know, only the smaller, in particular the capillaries and fine veins, are permeable. Consequently, the cohesion may be destroyed, or, in other words, a *solution of continuity* occur everywhere; an alteration of the permeability, *i. e.* a *diapedesis*, only in vessels of small calibre; unless indeed there be agencies capable of diminishing the consistency of the wall in vessels larger than those which are normally permeable. The latter view is, naturally, quite conceivable; and if the statements of Stroganoff* are universally applicable, it is, indeed, highly probable that in scurvy and purpura red corpuscles penetrate from the interior even of the aorta and other large arteries through the endothelium and reach the tissues of the intima, while from the vasa vasorum a diapedesis takes place into the outer layers of the vessel wall. Be this as it may, the small vessels are of chief consideration in the hæmorrhage by diapedesis into the tissues, cavities, or exterior of the body; and, on the other hand, it is they that are most readily ruptured by violence. But it need hardly be said that an agency which reduces the consistency of the vessel wall does not necessarily exalt its permeability, and *vice versa.* Temporary arterial ischæmia, and also exposure, render, as we have seen, the capillaries considerably more permeable; that they become more lacerable in consequence we have no proof. On the other hand, we *know* of the atheromatous process that it increases the brittleness of the vessels, and many *believe* the same of fatty degeneration; and yet there is absolutely nothing to indicate that their permeability is augmented through these changes of structure. This will seem to you no less intelligible from our standpoint than is the possibility of the existence of agencies which are attended by both effects, *i. e.* which favour *the tendency to ruptures and to diapedesis* in the same vessels.

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* Stroganoff, 'Virch. A.,' lxiii, p. 540.

But whether the bleeding has occurred by rhexis or by diapedesis its significance for the circulation is chiefly determined by the quantity of blood effused. Bleedings from the heart and from the large vessels, which, as repeatedly dwelt on, always originate in a solution of continuity, are usually so considerable that death is their immediate result. In rupture of the heart, the bleeding takes place, as a rule, slowly, owing to the gradual yielding of its thick wall. At first it is rather a *trickling* of blood in drops through the channel formed by the rupture; which latter only gradually becomes enlarged. Instead of death being caused by hæmorrhage, the filling of the pericardium with blood leads to stoppage of the heart's action before the amount lost could in itself prove fatal. It is, of course, implied that the hæmorrhage is not due to a wound which has opened both heart and pericardium. The bursting, or opening in any way, of large arteries and veins is followed under all circumstances by such profuse and copious bleeding that, unless artificial means be employed to check it, the individuals perish in a very short time from direct loss of blood. What quantity of blood may be lost by a person without fatal consequences naturally depends on his strength and constitution, and is liable to considerable individual variations. A strong man may recover after the loss of a large amount of blood; women can tolerate even still greater losses; while young children are highly sensitive in this respect. If other hæmorrhages have preceded, a fresh one will, of course, be more difficult to bear. The experience, which has been gained by producing hæmorrhage in dogs, is in general applicable to human beings. When a quantity of blood equal to 3·5—4 per cent. the body-weight is lost the animal is usually seized with convulsions, and perishes irretrievably. But even after a loss of 3 per cent. the body-weight many dogs fail to recover. But if an animal or a human being does not die as the result of severe bleeding, he becomes anæmic—a condition which will next occupy our attention. Small hæmorrhages amounting to a few grams, or even a couple of ounces, when occurring in a healthy adult are without any influence on the general condition.

The actual result of every solution of continuity of a blood-vessel, while the circulation is carried on without interruption, must finally be total depletion or a fatal hæmorrhage, *were it not that the majority of hæmorrhages cease spontaneously.* This is owing to the *coagulation* of the blood. When the blood has left the vessel it quickly coagulates, as you are aware; and if the forming clot is not at once swept away by the stream as it flows out, a plug is rapidly produced on the outside of the vessel wound. Yet this coagulum would hardly suffice to prevent all further escape from the aperture, and, in reality, it is not the clot *outside* the vessel that effects the closure of a tear or wound, but solely the *secondary thrombosis occurring in its interior.* The endothelium is absent at the seat of injury, and, as you have learned already, the blood must necessarily coagulate there. The best proof of the correctness of this explanation is afforded by the fact observed by Zahn,* that the thrombus occluding a vascular rupture is of the *white* variety. White corpuscles first become adherent to the borders of the aperture; on these new ones are superimposed, and this continues till finally the entire gap is filled up. The uninterrupted flow of blood from the opening does not, it is true, favour its closure, and so it may easily happen that the white thrombus will be repeatedly washed away while forming. Here everything depends on the energy of the stream and the pressure under which it flows through the vessel in question. Thus, in injuries to capillaries and small veins, the thrombus will always be sufficiently firmly established after a short time. But in solutions of continuity occurring in arteries and large veins, this result is much more difficult of achievement. In the arteries, the spontaneous *retraction of the wall* after a wound is of material assistance, so much so, that for an artery to be completely torn across or fully divided is more favorable to the stoppage of the bleeding than are longitudinal wounds or partial transverse division. But still greater importance attaches, both in arterial hæmorrhage and in bleeding from the larger veins, to the *lowering of arterial pressure* and feebleness of the heart which necessarily ensue on a considerable loss of blood. For as the pressure diminishes, the flow from the wound becomes less and less brisk, so that a sufficiently firm thrombus can be gradually established. So important is this factor that it would be improper to combat the general anæmia by transfusion immediately after the spontaneous cessation of such a bleeding, unless, indeed, care had in the meantime been taken to secure the firm closure of the vessel wound. But the formation of a thrombus after copious hæmorrhage is also favoured, though in a subordinate degree, by the change which is undergone by the blood itself in consequence of the bleeding. For since, as compared with the leucocytes (which mostly remain in the vessels of minute calibre), a large number of red discs escape from the wound, the blood after a severe hæmorrhage becomes relatively *rich in colourless corpuscles;* and, moreover, it is probable that the lymph, together with its cells, enters in large quantities the poorly filled vascular system, and thus adds to the number of the white blood-corpuscles. The immediate result of this is *an increased coagulability* of the blood, a point which may be very strikingly demonstrated in a dog bled to death by the removal of blood from a vein in successive portions; the *last* portions often coagulate almost *instantaneously*. Corresponding to the behaviour of the blood when drawn from a vein, is its tendency, while within the vessels, to form thrombi, by which the closure of the aperture and stanching of the hæmorrhage is favoured. For the rest, it need hardly be said that movement, warmth, a depending position, pressure on the efferent veins of the injured vascular area, must increase the bleeding, while cold, rest, an elevated position are of use in checking it; and that where the hæmorrhage takes place from contractile tissues, such as the uterus, the muscular contractions aid in its control. But above all it is the surgeon's art that avails here; and in the lectures on surgery you will receive precise instructions on the various means, direct and indirect, by which hæmorrhage may be checked.

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* Zahn, 'Virch. A.,' lxii, p. 81.

But whatever means be employed for this purpose, the agency by which the bleeding is actually stanched is under all circumstances the *thrombosis*. This not only brings about the spontaneous stoppage of a hæmorrhage, but, even after artificial occlusion by a ligature, it is by it that the *definitive* closure of the wounded vessel is effected. A ligature, whatever its material, must after a time cut through the vessel, slacken, or be resorbed; whereupon the bleeding would at once recommence, were it not that a thrombus has meanwhile formed at the seat of ligature. The details of this procees, and the subsequent fate of the thrombus—in particular the transformation into vascular connective tissue commonly undergone by it—have all been discussed on a former occasion. As the result of such a process, the lumen of the vessel becomes definitively interrupted, and the only paths by which the blood can pass from the portion of the vessel lying behind the wound into the portion beyond it are the collateral channels. Many of the thromboses by means of which the spontaneous stoppage of a hæmorrhage has been effected terminate in precisely the same manner. This is the case when the thrombus increases so as to fill the entire lumen, and does not subsequently become canalised. In many examples of wounds of vessels, however, the process stops short before a completely obstructive thrombus is formed; it then leads to the production of a slight protuberance on the wall, which, while it closes the rupture, allows more or less of the lumen to remain pervious. Moreover, these parietal thrombi generally undergo organisation; and there is left a mere trifling increase in thickness of that part of the wall where the aperture existed, which is attended by no evil consequences to the circulation through the vessel. This, the most favorable of all terminations, is occasionally observed in vessels of every calibre; even rupture of a capillary need not necessarily end in its destruction, while repair of wounds of the heart by this method has repeatedly come under observation. The preceding remarks refer exclusively, of course, to the true hæmorrhages by rhexis. For the stoppage of bleeding by diapedesis no special processes are required. It ceases on the disappearance of its cause, or when the permeability of the capillary wall is reduced to the normal standard. Since, however, capillaries from which even a copious diapedesis is taking place, differ in no way, as regards optical characters, from their fellows, one cannot expect to determine the phenomena of recovery by any microscopical test. In particular—and I desire once more to emphasize this point—the adhesion of the colourless blood-cells to that part of the wall through which the blood-corpuscles have passed, marking as it does in every case the commencing repair of a solution of continuity, is here absent.

But what, you will ask further, becomes of the effused blood? As far as the subsequent history of the extravasation is concerned, it is, of course, quite immaterial whether the hæmorrhage has occurred *per rhexin* or *per diapedesin*; for in both cases we are dealing with quantities of blood or of the constituents of blood, which lie outside the vessels, and which naturally will now experience the same fate. I need hardly say that blood escaping from the vessels of a superficial wound simply flows away in an outward direction; but precisely the same occurs in hæmorrhages into cavities which freely communicate with the exterior, and from which the blood easily escapes, as the cavum uteri, the cavity of the pharynx, the pelvis of the kidney, &c. On the other hand, should the effused blood meet with impediments to its outward progress, as would occur, for example, in bronchiectases or in a uterus with stenosis of the os, the extravasation behaves like one occupying a pre-existent closed cavity. The subsequent history of these internal hæmorrhages does not, however, differ in any respect from that of the bleeding taking place, not into pre-formed cavities, but into the substance of the tissues. For even the presence of masses or shreds of tissue such as are invariably found in hæmatomata and circumscribed hæmorrhages, does not essentially affect the fate of an extravasation, since such material is incapable of progressive change and is doomed to perish and disappear; the same may be said of the necrotic tissue of a hæmorrhagic infarct.

The admixture of particles of disintegrated or necrotic tissue is less worthy of consideration than is the size of the extravasation; for small bleedings are, naturally, more easily dealt with by the organism than are large ones.

But, with regard to the immediate fate of the effused blood, it is quite unimportant whether it be considerable or inconsiderable in amount; the first change is invariably coagulation, and the tissues destined to disintegrate are included in the coagulum. Whether the whole of the effused blood or only a portion of it coagulates, leaving a smaller or larger quantity of fluid, appears to depend essentially on its localisation. A cerebral hæmorrhage, when recent, is found, as a rule, in the form of a voluminous, coherent mass of blood without any fluid portion worth mentioning; while in hæmorrhages into serous cavities or joints* a not inconsiderable quantity is wont to remain fluid. This fluid part of the extravasation disappears with comparative rapidity, being taken up and carried off by the lymphatics; that is, it is removed by simple absorption. From the peritoneal, and no doubt from the thoracic, cavity also there passes in so short a time so considerable a quantity of blood with unaltered corpuscles through the ductus thoracicus into the blood-vessels, that on the strength of this fact a method of *peritoneal transfusion* has recently been devised. Yet even in effusions into the extremities it has been shown in Orth's institute† that a portion of the extravasated blood with its corpuscles regularly passes through the lymphatic glands, and in this way returns to the circulation; though another portion, it is true, is retained in these glands, and there undergoes that metamorphosis into pigment, soon to be described. It appears, however, to be very rare for large quantities of blood-corpuscles to remain a length of time in the lymphatic glands so as to produce considerable swelling of the latter, and lend to their interior a blood- or dark-red aspect.‡ The coagulated extravasation also is diminished in volume by the gradual absorption of its watery constituents; and in consequence, the entire mass becomes denser, more compact. To this the coagulation is no impediment, for it does not persist; the fibrinous portion of the effusion is soon liquefied and likewise undergoes absorption. Moreover, the colourless corpuscles at first contained in the extravasation are not abiding; many no doubt perish during coagulation, and the remainder appear regularly to forsake the clot, by being extruded perhaps, or it may be by spontaneous locomotion. The entire interest centres, therefore, in the fate of the *red* corpuscles, and their fate may be very different. For while many of them are still carried off by the lymphatic stream, many others are becoming *decolourised* in such a way that the colouring matter is diffused in the neighbourhood, leaving the colourless stroma behind. The stroma itself, it seems, very quickly disappears, either by simple liquefaction or by disintegration. The occurrence of this decolourisation, which progresses from the margin to the centre of each disk, has been established beyond doubt by J. Arnold* for the corpuscles of the frog; and it cannot therefore reasonably be questioned that it also occurs in the blood-corpuscles of mammals and man, although here it is certainly more difficult to determine.† But the peculiar, distinctly transparent colour, like that of a saturated ammoniacal solution of carmine, which, for example, an apoplectic patch in the brain commences to assume from the fourth or fifth day, is itself sufficient evidence of an extensive separation of the colouring matter from the blood-corpuscles, or of a solution of the latter. Moreover, we know how the colouring matter set free is disposed of. It also in great part suffers simple resorption, giving rise to an excretion of urobilin, a substance which recently has been repeatedly detected in the urine after large internal hæmorrhages.‡ In part, however, it is transformed into crystalline hæmatoidin; a few days apparently sufficing to bring about this change in man, and a still shorter time in the dog. These are oblique rhombic crystals, at most 0·1 mm. long, and of a yellowish-red or brick-red colour; but we also meet with orange-yellow needles and small angular, or jagged, rust-coloured particles, consisting of hæmatoidin, but less perfectly crystallised.

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* Penzoldt, 'D. A. f. klin. Med.,' xviii, p. 542; Riedel, 'D. Zeitschr. f. Chirurg.,' xii, p. 447.

† W. Müller, 'Untersuchungen über d. Verhalten d. Lymphdrüsen bei der Resorption von Blutextravasaten,' I.-D. Göttingen, 1879.

‡ Orth, 'Virch. A.,' lvi, p. 269; Tillmanns, 'Arch. d. Heilk.' [illegible], *p. 119*; cf. also Hindenlang, 'Virch. A.,' lxxix, p. 492.

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* J. Arnold, 'Virch. A.,' lviii, p. 231; Lange, 'Virch. A.,' lxv, p. 27.

† H. Cordua, 'Ueber den Resorptions-Mechanismus v. Blutergüssen,' Berlin, 1877.

‡ Cf. Kunkel, 'Virch. A.,' lxxix, p. 455.

While, then, hæmatoidin is formed, according to the unanimous belief of all writers, from the free colouring matter of the blood, *without any aid from the cellular elements*, the latter take an active part in determining the history of extravasations in another way. The red blood-cells are taken up by the lymph-corpuscles, which very quickly collect in the immediate neighbourhood of an extravasation and penetrate into its interior, the result being the formation of the much discussed blood-corpuscle-holding cells. The included blood-corpuscles are almost never discoidal, the vast majority having previously become globular. Nor does the material taken up always consist of entire corpuscles; it may be composed of small roundish particles, produced by the early disintegration of many of the corpuscles, such as may be secured in identical fashion when the red discs are treated by artificial means, exposure to extremes of temperature, &c., and split up into hæmoglobin-drops. On the other hand, some lymph-cells, it is true, contain only *one* blood-corpuscle or fragments of one, but many of them contain several, even as much as ten or more. This naturally involves a large increase in the volume of the blood-corpuscle-holding cells, which may, indeed, be ranked with perfect giant-cells. As you observe, we here again notice what we first became acquainted with in connection with productive inflammation, namely, that colourless corpuscles grow by consuming any material that happens to be at hand, for of course it is not impossible that an enlargement of individual lymph-corpuscles at the expense of others may also take place here; these would become multinucleated giant-cells, and only then perhaps commence to feed on the red corpuscles. Accordingly, it is not surprising that blood-corpuscle-holding giant-cells should not be met with till the later stages of an extravasation—about the end of the first week after the bleeding has taken place. The essential interest of these blood-corpuscle-containing cells undoubtedly consists in the fact that by their agency the metamorphosis into a *pigment* containing iron is effected. For, as demonstrated by Langhans,* it is precisely the blood-corpuscles contained in lymph-cells that shrivel up and acquire a darker hue, and are thus transformed into reddish brown, roundish, or more angular bodies of varying size, which occupy the interior of the cells in numbers more or less great. The subsequent fate of these pigment-containing bodies must be sought in one of two directions: the cells may perish by fatty metamorphosis when *the granules and flakes of pigment are set free*; or the latter may divide and redivide into finer and finer particles, till ultimately they are completely *dissolved* in the cell contents, imparting to it a *diffuse yellow colouration*, which is subsequently lost. According to this view, of which Langhans is the most logical representative, the transformation of the red blood-corpuscles into pigment is always *intracellular*, occurring in the interior of cells, and precedes the diffuse imbibition of the lymph-corpuscles with colouring matter. According to the older doctrine laid down by Virchow† in a celebrated communication, the pigment originates partly by the direct transformation of *free* red blood-corpuscles—is *extracellular* in its origin—and partly by the solution of some of the red corpuscles and the absorption of the dissolved colouring matter by the lymph-cells, which then give rise to the pigmented cells. With regard to the first modus, or the free extracellular formation of pigment, Langhans has admitted its possibility, and merely urges the want of evidence for its occurrence. On the other hand, he has dwelt, I think correctly, on the improbability, according to the present state of our knowledge of cell-life, that living cells should undergo imbibition by a fluid, a solution of colouring matter. On the latter point Cordua,‡ the most recent investigator of this question, agrees with Langhans; while, on the other hand, he strongly advocates Virchow's doctrine of a direct pigment-metamorphosis from red blood-corpuscles.

But, however this may be, the residue remaining after an extravasation of some weeks' standing, if there be any residue, consists solely of hæmatoidin-crystals, pigmented cells, and free granules and flakes of pigment. This is, it is true, the most favorable possible result, and cannot be looked for with any certainty except in small hæmorrhages. The latter, however, are accustomed, except for the traces before mentioned, to disappear completely; indeed the particles of pigment and the crystals of hæmatoidin, though of a much more enduring character, may in the course of months or years gradually undergo complete absorption, and leave absolutely nothing to indicate the former presence of a hæmorrhage. Hardly so innocent is the course taken by most large effusions, at least in cases where the extravasation is confined within a limited space. For where blood is effused over an extensive surface it may in the end disappear totally, even when the quantity has been very considerable. In a circumscribed hæmorrhage into the tissues, or in a well-defined hæmatoma, the contrary is the case; direct resorption is almost never completely effected; and the residue must of necessity act as a foreign body, *i. e. excite an inflammation in the surrounding parts.* The inflammation is, of course, also attended by danger; for example, where a patient has survived the immediate effects of a cerebral hæmorrhage, inflammation may subsequently bring about the fatal termination. As a rule, however, when moderate in degree, it leads to other changes of a highly favorable nature. It is then of the *adhesive* variety: new vessels develop, grow into the coagulum, and with the assistance of immigrant colourless blood-corpuscles, initiate and complete its organisation in identically the same way as we found it occur in the organising thrombus. The two cases are exactly similar; for here, as in the thrombus, the new vascular connective tissue, which is at first gelatinous but afterwards more consistent, is substituted for the extravasation; while the latter takes no part in tissue-production, but gradually contracts and recedes before the advance of the new tissue from the periphery. When organisation is completed in this way, the total resorption of the effused blood, though delayed, is eventually brought about. This termination is often observed in hæmorrhage into muscles, in bleeding as the result of tenotomy, and very beautifully in the cephalhæmatoma of the new-born;

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* Langhans, 'Virch. A.,' xlix, p. 66.

† Virchow, ibid., i, p. 379, iv, p. 515.

‡ H. Cordua, 'Ueber den Resorptions-Mechanismus v. Blutergüssen,' Berlin, 1877.

the product of organisation in the last case being bone, and not connective tissue. The cicatrix which takes the place of a hæmorrhagic infarct in the spleen or kidney is also mainly the product of its organisation. It more commonly happens, however, that organisation remains incomplete, being confined to the peripheral zone of the extravasation; as, for example, in hæmorrhage in the brain, the thyroid, and more especially in tumours. In these cases the persistent central mass, after having in part undergone the metamorphosis into pigment, both free and contained in cells, as well as into hæmatoidin, usually liquefies after a time, thus giving rise to so-called *apoplectic cysts*. The latter are cavities bounded by a connective-tissue capsule, and filled with a reddish-yellow to greyish-yellow emulsion-like fluid which gradually becomes more and more watery. What was once an extravasation may remain for years in this condition; the residue of pigment and hæmatoidin being about the only thing to indicate its true character. Yet even then a further resorption of fluid is not impossible, in which case we have as sole remnant of the hæmorrhage the *apoplectic cicatrix*. The latter, as will readily be understood, may also result directly from the transformation of a circumscribed hæmorrhage, without the interposition of a cystic stage. In this way a really considerable accumulation of blood may finally be converted into a hard, irregularly-shaped band or membrane, the rust colour of which alone indicates its origin.

In very rare cases an extravasation may *dry up* or *become cornified*. Occasionally a deposition of *lime-salts* has been observed, leading to the transformation of the hæmorrhage into a chalky concretion. But a much more important change is the establishment in the extravasation of *putrid decomposition*, the facilities for which are very great in organs freely accessible to the atmosphere. Hence it is that pulmonary hæmorrhagic infarcts are always more dangerous than those of the spleen or kidney; and for the same reason we shrink from depending on the slow process of absorption for the removal of a uterine hæmatoma. For when a pulmonary hæmorrhagic infarct undergoes putrid decomposition, the inflammation arising around it is not productive but *purulent*; it becomes *dissecting*, as it is called, and may very readily be complicated by a severe pleuritis. Even a profound blood-poisoning, a *septicæmia*, may, it is evident, be the result of the putrid decomposition of an extravasation.

Having so thoroughly discussed the history of extravasations, we need say but little now as to the significance of hæmorrhage *for the organs involved in it.* It may be stated generally that it is not so much the effused blood itself that produces a pathological effect on the organ in question, but rather the *disintegration of the tissues* taking place *pari passu* with the bleeding. On the latter factor depends the importance of a hæmorrhage for the organic function; although bleeding may be productive of very considerable disadvantage, either by its pressure, when occupying a part enclosed in solid, unyielding, or only slightly distensible walls, or by plugging a narrow channel, *e. g.* the ureter. As far as the extravasation extends the original tissue of the part is lost, and must be regenerated or newly formed after the hæmorrhage is removed. Now, if the affected organs admit of the loss of part of their substance without detriment, or readily allow of repair, as do, for example, the epithelium of the skin or mucous membranes, many muscles, and all kinds of connective tissue, even a large effusion of blood is of no great importance. On the other hand, an ecchymosis is for the retina a serious event, and in the medulla oblongata an extravasation no larger than a pea is enough to seriously imperil life itself. But hæmorrhage into the central nervous system is chiefly of such grave import because, owing to the impossibility of a regeneration, the consequent loss of nerve-fibres and cells is irreparable and definitive.

CHAPTER VII.

PLETHORA AND ANÆMIA.

Physiological regulation of the quantity and composition of the blood so as to maintain the normal standard.—Artificial plethora.—Experiments.—Explanation.—Effects and consequences of artificial plethora.—Removal of the superfluous blood from the organism.—Impossibility of a permanent plethora vera.—Polyæmia of the new-born.

Effect of a moderate loss of blood on the circulation.—Regulation of blood-pressure.—Regeneration of the blood.—Influence of a severe loss of blood on the blood-stream.—Transfusion of blood of the same and of a different species to that of the recipient.—Transfusion of an alkaline solution of common salt.—Constitution of the blood after severe hæmorrhage.

WE now turn to the last group of circulatory disturbances—those which are conditioned by *an alteration in the blood.* For, that the circulation may proceed normally it is necessary, not merely that the condition and function of the heart and vessels should be normal, but that the blood also should be of normal quantity and constitution. And just as we occupied ourselves in thoroughly examining the effects exerted on the circulation by changes in the action of the heart and condition of the vessels, so we shall now have to discuss a question of no less interest, namely, the consequences to the circulation *of morbid alterations in the quantity and composition of the blood.* By putting the question in this form we at the same time map out our course; we shall first carefully analyse the *quantitative,* and afterwards the *qualitative,* deviations of the blood from the normal standard.

But though the problem we have set ourselves is apparently a simple one, a little thought will show it to be involved in difficulties that demand careful attention. These centre in the fact that the blood is *an unstable fluid of varying composition.* It is not merely that it participates in all the changes affecting the organism as a whole, losing in general marasmus and gaining with the increase of the body generally; for in speaking of a normal blood quantity we refer not to an absolute standard but to a relative one, and therefore expect to find the blood of a debilitated, emaciated individual reduced in the same degree as his heart has atrophied. But the blood is a factor which is normally liable to constant variations, even when the heart and vessels remain perfectly intact. Fresh substances and fluids are constantly supplied to the blood; its elements are constantly undergoing regeneration; and its constituents are no less constantly being consumed. A moment's reflection will make it clear to you that *the quantity of blood in the same individual must vary within very short intervals.* Some little time after an ample meal, or after partaking largely of liquids, the quantity of blood circulating in the vascular system will be greater than before. More than this—its composition will be altered; for since the nutriment taken by us has a different composition to that of the blood, and we therefore supply to the latter with the chyle a fluid of different constitution, its composition as a whole must necessarily be affected. Furthermore, there is a continuous interchange going on between the blood and the fluids bathing the vessels. Any alteration of transudation, whether dependent on glandular secretion, muscular movements, or pathological causes, must necessarily influence the quantity and constitution of the circulating blood. No less important is it for the latter, when conversely the tissue-juices, the lymph, transudes into it through the walls of the capillaries, as happens whenever the tension of the blood is less than that of the surrounding fluid, or whenever blood and lymph contain substances of different diffusibility in solution.

Still we are fully justified in regarding a certain quantity of blood as *normal,* and you find in the text-books of physiological chemistry analyses of the blood of various healthy individuals which differ only to a most trifling extent. I need hardly tell you how this is to be explained. It is the well-known capacity of the organism for adapting itself to various changes, its *regulative mechanism*, which in a normal state allows of the blood being maintained in an average condition, qualitatively and quantitatively. If the amount of blood is increased by dilution resulting from the abundant absorption of water, there follows an increased excretion of urine, &c., which continues till the blood is restored to its normal concentration and amount. If, on the other hand, the blood loses much water by copious perspiration, the sensation of thirst very quickly warns us that the fluids of the tissues have entered the blood in such quantity as was necessary to cover the loss. On the increased supply of albumen there promptly ensues an increase in its decomposition, and if you introduce a foreign material, such as iodine or curare, into the blood, you immediately find it in the secretions, urine, saliva, &c. However greatly you may vary your experiments, you will not succeed in causing the quantity or composition of an animal's blood to continue abnormal for any length of time. There takes place in the blood under physiological conditions at all times an extraordinarily prompt and sure regulation *having the tendency to maintain the normal quantitative and qualitative standard.* The organism requires a certain amount of blood having a certain constitution in order to discharge its functions; if a portion is lost, fresh blood is prepared in the proper localities. On the other hand, the organism will not maintain more blood than it needs; should the quantity become excessive for any reason, the superfluous part is removed by increased consumption and excretion.

But although the foregoing facts all harmonise thoroughly, and it can hardly be doubted that in presence of physiological conditions the regulative mechanism of the organism suffices constantly to maintain the blood at its normal standard in point of quantity and constitution, we are not therefore warranted in assuming that under pathological conditions this end can always be secured with the same certainty. Who would venture to say, for example, whether, when through some cause or other the amount is increased *by a very considerable addition*, the superfluous blood is removed? The only means of arriving at a positive decision on this point is experiment;

nor, of course, is there the least difficulty in increasing the blood-quantum of an animal artificially. An experiment of this kind ought to be all the more profitable, as we should at the same time learn from it what influence a possible abnormal increase in the amount of blood can exert on the organism as a whole and on the circulation in particular. Blood may be introduced directly into the vascular system of a dog from a second animal by connecting the carotid of the one with the central end of the vena jugularis of the other; or a quantity of blood may be taken from an artery or vein of one animal, and injected by means of a syringe into one of the venous or arterial vessels of the other. In the latter case it is advisable to defibrinate and strain the blood before injecting, in order to avoid any disturbing complication that might arise from clots; and if an accurate experiment be desired, the preference should be given to the latter procedure (although in it defibrinated blood is introduced) because it allows us to control the pressure with which the blood enters, and especially because we are enabled to determine the amount injected with perfect accuracy. A middle-sized dog with good blood-pressure should be chosen. The carotid is connected with the kymograph during the curare- or opium-narcosis, and into the central end of the v. jugularis or v. femoralis a measured quantity of freshly-whipped dog's blood heated to 38° C. is injected. The course of events will regularly be as follows. During each injection, however carefully and slowly made, you see the carotid pressure rise by 20 or 30 mm. mercury, or even more. But the rise does not last long; after a few minutes the old level is again reached. The operation may be repeated a few times, and always with much the same result. You may find even that between the injections the pressure suddenly falls below its original level, only, however, to reascend very rapidly. Yet if you continue injecting till about half the normal blood-quantum, or 3—4 per cent. the body-weight, has been introduced, the pressure is usually maintained at a very high value, 170 or 180 mm. Hg.,—a value that is, which may possibly be somewhat higher than the original, but which is still strictly within the normal limits. And now, although the injection be repeated a few times, *the mean pressure does not rise a single millimetre.*

You observe the curve ascending during each injection, but no less constantly does it fall during the pauses; the only change being that the period which elapses before the elevation of the curve again recedes is prolonged in proportion to the amount already transfused. You may continue injecting till you have doubled the blood-quantum of the animal; you may indeed introduce 10 or even 12 per cent. the body-weight without perceiving any change of the blood-pressure curve other than those enumerated; but should you persist still further, you will be surprised by *very considerable ascending and descending oscillations of pressure* during the next following injections, which without exception indicate a speedy termination in death. I myself have never seen a dog survive the experiment, when 14 to 16 per cent. the body-weight, or about double the blood-quantum, had been transfused, and as a rule animals into whose vessels an amount greater than their own blood-quantum has been introduced perish in the course of the same or following day, even though to all appearance they have borne the operation well. Death is still more likely to follow the introduction of one and a half times the normal blood-quantum. Worm Müller,* who was the first to investigate the question of plethora in a systematic series of experiments carried out in Ludwig's laboratory, states that an addition to the blood of 150 per cent. is the outside limit, beyond which life is directly threatened.

The experiment takes a slightly different course when carried out on an animal whose blood-pressure is low to commence with, as, for example, a dog from whom a considerable quantity of blood has previously been withdrawn. Here the first injections are each accompanied by a lasting elevation of pressure, which continues to rise till the high normal values are reached. Afterwards, however, the experiment has precisely the same features as the preceding one, *i. e.* the elevation of pressure occurring at each injection disappears during the pause. The cardiac pulse-rate, we may state in this connection, remains absolutely unaffected in all these transfusion experiments, or if it be affected, this at least is not the rule. Occasionally, you see the pulse-rate accelerated in the middle of the experiment, shortly afterwards a little retarded; often no change whatever is experienced. If irregularities in the rhythm or intermissions set in, it is a sign that the end is approaching.

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* Worm Müller, 'Ber. d. Leipz. Ges. Math.-Phys. Kl.,' 1873, p. 573; 'Transfusion und Plethora,' Christiania, 1875.

How are these experimental results to be interpreted? The results are, I repeat, quite constant and regular, however paradoxical it may seem at the first blush that the arterial tension should not stand in any direct relationship of dependence to the quantity of the circulating blood. That the tension is absolutely independent of this factor cannot of course be credited; an increase of the amount of blood in the body is well adapted for the compensation of the effects of such agencies as abnormally lower the blood-pressure. But how, when the blood in the arteries already flows under a high tension, does the organism contrive that an augmentation of the blood-quantum shall not be followed by an *abnormal* rise of pressure? What means has it at disposal which enable it to regulate the *blood-pressure* so as to preserve the normal standard? Now, the rapidity with which the rise gives place to a fall immediately after the injection makes it probable *a priori* that *nervous* influences are the agents here. Whether some of the vaso-constrictors cease to be excited or the activity of certain of the dilators is increased, at any rate it is evident that additional space is supplied for the larger quantity of blood by relaxation of the tonic contraction of the arteries, and that the resulting diminution of resistance suffices to compensate for the increase in volume, thus maintaining the normal state of things in presence of a factor which would otherwise raise the pressure. The importance of this intervention on the part of the nervous system is most strikingly shown by the behaviour of animals during transfusion, when the cervical cord has been previously divided. In them the return to the former pressure after each injection is absent; the tension in the carotid slowly mounts in exact proportion to the quantity injected. Still the action of the nervous system is inadequate to explain the absence of all supernormal elevation of pressure on increasing the blood-quantum. For even after division of the cervical cord it is impossible to raise the arterial pressure at will by continuing the injections; *the tension does not exceed* *a certain value*, more or less nearly approaching that which prevailed before the cord was divided.

Accordingly, some other factor must be present—one which checks an abnormal elevation of pressure in excessive repletion of the vascular system. For the transfused blood at first remains in the interior of the vascular system, and it cannot for a moment be supposed that the vessels are relieved by an increase of transudation. True, as was shown by W. Müller, more lymph is produced than before, and during the injections and subsequently a larger quantity of more concentrated lymph flows from the ductus thoracicus—as you will notice, without any apparent dependence on the height of arterial pressure. But, in the first place, this augmentation in the quantity of lymph by no means occurs in all the organs; *e. g.* the skin, muscles, and indeed extremities generally are free from it. In the second place, the increase in the lymph-stream through the ductus thoracicus does not supply any additional space for the blood. To unload the vascular system it would be necessary for a certain part of its contents to enter the tissues or some one or more of the cavities, in short, to *forsake the blood- and lymph-channels*; and practically speaking, such an occurrence does not take place in these experiments. In animals into whom 8, 10, even 12 per cent. the body-weight has been introduced, there is found only—a trifling œdema of the pancreas with a few punctiform hæmorrhages of the organ; a slight bloody ascites; further, ecchymoses in the stomach and intestines: and the total amount of extravasated fluid, if estimated, will never be found to be more than 20 to 30 grams at most. If, then, the whole of the injected blood, save an insignificant fraction, remains in the vessels, the over-filling of the arteries beyond the natural tension can be avoided only by the disposal of the excess in other parts of the vascular system. These parts are the *capillaries* and *small veins*, chiefly, it would seem, of the abdominal organs. In animals which have been treated in the manner described, these organs always give one the impression of decided hyperæmia, while the extremities, skin, subcutaneous tissue, and central nervous system show no excessive vascular fulness. During and subsequently to each injection, the blood, having passed through the lungs, arrives in the aortic system; hence the pressure rises and continues high till the excess has been carried into the capillaries and venous radicles, when it again falls to normal, and remains so till the next transfusion once more causes its elevation. The *gradually increasing delay* in the return of the arterial pressure to its normal level after the later injections is quite in harmony with this explanation, for the fuller the capillaries are already, the more difficult is it for the arterial pressure to force new blood into them. On the other hand, this view is not invalidated by the fact that the pressure in the large veins does not permanently ascend beyond the normal value. During the injection it also rises, it is true, and sometimes very considerably, but this proceeds apparently from the resistance which the heart, being overloaded at the moment, opposes to the venous stream, as is most strikingly evidenced by venous pulsation, which usually appears during the injection, and immediately afterwards again gives place to the equable non-rhythmical flow. But not only does the venous pulse cease; the pressure also falls in the pauses, and even in very marked plethora sinks almost to its original level. This is possible because the over-filling does not so much concern the large veins, in which alone the blood-pressure can be measured, as the capillaries and venous radicles; and also because, owing to the great distensibility of the walls of the veins, a considerable addition to their contents need not raise the tension in them to any great extent—so long, at least, as *the entrance of venous blood into the heart is not impeded*. But during the intervals between the injections, when the arterial pressure has again become normal, the blood is perfectly free to enter. The quantity of blood now arriving in the heart is neither more nor less than before. For since the motor forces and the resistances have undergone no alteration, there is nothing to cause a more rapid flow, and no reason why more than the normal quantity should be conveyed into and out of the heart. These inferences are fully confirmed by microscopic observation of the circulation in the tongue or swimming-membrane of a frog, into the v. abdominalis mediana of which an injection of frog's blood is made. During its introduction an acceleration of the flow is of course present, and this must bring about an acute augmentation of the arterial pressure; very soon after the injection is completed the blood-stream regains its original velocity. Precisely similar results may be arrived at by determining the quantity of blood leaving the foreleg of a dog before, during, and immediately after transfusion.

This then is the modus by which a supernormal elevation of arterial pressure is obviated in over-filling of the vascular system. The fulness of the arteries themselves is not much increased, or is increased at most in so far as a moderate relaxation of tonus permits. The *capillaries and small veins*, chiefly of the abdominal viscera, become *filled to distension*, and so harbour by far the greater part of the superfluous blood. That this should be at all possible cannot be a matter of surprise to you, inasmuch as I have repeatedly directed your attention to the fact that the vascular system is vastly more capacious than the accommodation of the normal blood-quantum demands. How far its capacity reaches will be clear from other experiments which I shall very soon communicate to you. But although, as we have seen, space is provided in the vascular system for an abnormal blood-quantum, it would not therefore be justifiable to regard the excessive distension of the vessels in question, or as W. Müller terms it, their *elastic stretching*, as a perfectly harmless occurrence. This writer has brought forward a striking proof that the functional power of the vascular system is essentially lowered by very pronounced plethora. Venesection of a dog in whom artificial plethora has been produced causes the arterial pressure to fall so rapidly that it is found impossible to obtain even the quantity of blood originally introduced; the dog dies although he has more blood in his vessels than he possessed before the injection. This cannot really depend on anything but the decided impairment, from over-filling, of the elasticity of those portions of the vascular system which are situate between the arteries and the auricles, *i. e.* the capillaries and veins. Whether it is to the gradually increasing enfeeblement of elasticity in these vessels that the death of the animals is ultimately due when the plethora is continuously increased, I shall leave undecided. A definite, tangible cause of death can no more be found in the cases where the dogs have perished during the experiment than in those where they have survived it some hours or even days. During this period the animals with the extreme polyæmia exhibit various morbid symptoms, such as vomiting, hæmaturia; they have no appetite, are exhausted and decidedly decrepit, till death ensues without any phenomena of a striking character.

None of these symptoms are observed in dogs, the over-filling of whose vascular system has been *moderate in degree.* Far from confirming the apprehensions with which older medicine regarded over-filling of the vessels, however slight, the experiments of Lesser,* W. Müller, and others have demonstrated that dogs into whom a half, or even two thirds, their original blood-quantum and more, has been injected show absolutely no disturbance. They run about briskly after the operation, and feed with a good appetite; and Lesser was able in the space of a week to transfuse into the same dog, on the first occasion 81 per cent., and on the second 75 per cent. its blood-quantam without any morbid results. But though this fact is sufficiently remarkable, you will be still more interested in the question—*what becomes of the injected blood?* W. Müller has endeavoured to answer it by systematically examining the blood, and by investigating the metabolism, in so far as this is manifested by the urine. He starved the dogs before and after transfusion, determined the number of corpuscles present in the blood by the method Malassez,† counting them prior and subsequently to the injection during several days, and at like intervals estimated the amount of urine and contained urea. By comparing the results got by counting the blood-corpuscles with previous calculations he could arrive at perfectly harmonious conclusions, provided, of course, that the injected blood was equally distributed throughout the blood of the animal. That this actually happens cannot reasonably be doubted, the more so as the intermixture of the blood with a liquid even of quite dissimilar characters is, as you will soon learn, fully effected in a very short time. The result arrived at by W. Müller was quite constant. He found that a very considerable portion of the injected plasma passes out of the vessels during the next few hours. The remainder of the foreign plasma is not disposed of so rapidly; but after two or three days no part of it could be detected, even when 60 or indeed 80 per cent. the original blood-quantum had been transfused. He now invariably found the number of the blood-corpuscles to correspond pretty accurately with the total obtained by calculation from the original and the transfused blood. But the increase of corpuscles is also evanescent; a few days after the injection they begin to disintegrate, and, more and more of them becoming gradually involved, the result is that after a few weeks at farthest they are not more numerous than before the operation. The time required for this destructive process depends, of course, on the amount of blood transfused. After injections of from 20 to 30 per cent., the whole of the new blood-corpuscles are destroyed in a few days; when from 60 to 80 per cent. has been introduced, two or even three weeks must elapse before they are completely removed. As to the means whereby this retrogressive alteration of the blood to the normal is effected the urine offers the most important information. This excretion and the contained urea are augmented from the day of transfusion; but while the increase in the amount of urine is not maintained at its original value, the excretion of urea remains excessive till the injected blood-corpuscles are totally destroyed. Whether any of the other gaseous or liquid excretions are increased has not yet been determined, though this is probable enough. But the facts adduced are sufficient to establish the view *that the blood artificially transfused is destroyed in the organism*, the plasma more quickly than the corpuscles; and that the products of its destruction appear in part in the urine. Some of these products which are not excreted by some channel or other remain, as Quincke* has recently shown, in the form of yellow or brown granules of varying size. These granules all give the reaction of iron with the greatest readiness, and occupy the liver, the spleen, and the medulla of bone. In the liver the ferruginous granules are enclosed in leucocytes situated in the interior of the capillaries; while in the bone-medulla and spleen, on the contrary, they are contained in the cells of the parenchyma. I do not apprehend that any of you will attach less importance to these experimental results because they have been obtained by the transfusion of defibrinated blood. For there is nothing in the nature of the case to lead one to anticipate that the presence or absence of a number of colourless corpuscles, and of the exceedingly minute quantity of fibrinogen which the normal blood contains, could in any way influence the fate of its remaining, greatly preponderating, constituents. Moreover, the results of direct transfusion from the carotid into the jugular have been proved to be fully in accord with the foregoing.

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* Lesser, 'Ber. d. Leipz. Ges. Math.-Phys. Kl.,' 1874, p. 153.

† L. Malassez, 'De la numération des globules rouges du sang,' Paris, 1871.

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* Quincke, 'Festschrift zum Andenken an Alb. v. Haller.,' Bern, 1877, p. 37; 'D. A. f. klin. Med.,' xxv, p. 567, xxvii, p. 193.

The truth of the views which we have placed at the head of our discussion on plethora could not be more forcibly proved than by these experiments; and whoever has witnessed them will, I think, henceforward treat with some distrust all statements in favour of the existence of a lasting pathological increase of the blood-quantum. In the older literature, it is true, no unimportant part is played by *plethora vera* or *polyæmia;* and many pathologists of eminence still unhesitatingly maintain its genuineness. It will hardly be held by anyone nowadays that the disappearance of habitual hæmorrhages, such as the menstrual or hæmorrhoidal, could give rise to an abnormal increase in the blood-quantum; for the non-occurrence of the bleeding results simply in the absence of the corresponding blood-regeneration. Nor can the form known as *plethora apocoptica*, supposed to arise in consequence of the removal of one of the larger parts of the body, *e. g.* after amputation of an extremity, be said to have any supporters at present. For though it has confidently been claimed that individuals who have lost an extremity complain after a time of various congestive conditions and other troubles pointing to over-fulness of the vascular system, this is, nevertheless, incorrect; and even if it occurred, should be interpreted in a very different way. When an extremity is removed, perhaps without the loss of a drop of blood, the organism, by increasing its gaseous and liquid excretion, consumes and disposes of such a quantity as, owing to the absence of the extremity, has become "*superfluous.*" For the future too it is able to keep the blood-quantum within its normal relative limits; the more easily since, in addition to the blood-consuming portions of the extremity, *e. g.* the muscles, the bone-marrow, a tissue engaged in producing blood, is also lost. There remains then but one other variety of plethora, that which is said to arise *in consequence of a superabundant supply of nourishment in persons of sluggish habit, especially if insufficient exercise be taken.* It is the polyæmia depending on these causes, the possibility, or rather comparatively common occurrence, of which is still looked upon by some clinicians as unquestionable. And yet a pathogenesis of this kind appears to me to be more than any other incompatible with what we know of the life and functions of the body and of its individual organs. Or can we really believe that the activity of the blood-producing organs may be enhanced at will by supplying albumens, &c., in the food, or that the body stores up as blood whatever portions of food are not needed for other purposes? On the contrary, we know that an excessive supply of nourishment excites in all cases a correspondingly abundant excretion; and that, even when the organism is not in a position to increase oxidation in adaptation to this supply, the most that results is an *abnormal production and accumulation of fat.* And now what are the symptoms cited in proof of overfilling of the vascular system? A full pulse, a florid, red countenance; a tendency to congestions of various organs on the one hand, and to passive hyperæmia and stagnation on the other; and, lastly, the development of cardiac hypertrophy in the absence of any other known cause—these are the factors on which the diagnosis "plethora" is based. Yet they bear no resemblance to the symptoms presented by animals in whom plethora has been artificially produced; and there is no difficulty in arriving at an equally satisfactory explanation of the conditions present by referring them to very different causes, *e. g.* to disturbances of innervation of the vascular system. I do not doubt for a moment that the same writers* who confidently speak of a plethora of gourmands, as though dealing with an axiom of physics or mathematics, would, if directly questioned, at once confess that the scientific evidence for this form of plethora is practically *nil*. But until proofs are produced, it may be well for us to adhere to the sceptical attitude justified by plain experiments on animals, and to refuse to relinquish our position *that a true simple polyæmia cannot under any circumstances be more than a mere transitory condition.*

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* *Vide e. g.* A. Fraenkel, in the review of the first edition of these lectures, 'Zeitschr. f. klin. Med.,' ii, p. 722.

I intentionally emphasize the *duration* of the plethora; for a remarkable fact has quite recently been discovered, namely, than an over-filling of the vascular system, a typical polyæmia, very frequently occurs as a transitory condition in the new-born—quite independently of a rapid and excessive supply of fluids, &c., from the digestive tract. Schücking* was the first to show (and his observations have since been confirmed by several obstetricians)† *that a large part of the blood of the fœtal placenta is forced into the vascular system of the child* by the contractions of the uterus, especially in cases where the second stage of labour has been tedious. The amount thus transfused into the child is far from small; different writers have determined, by weighing, an excess of as much as 100 grams and more, or more than half the average normal blood-quantum of the new-born. But the further course of what may be regarded as a plethora-experiment devised by nature herself is throughout identical with those which you yourselves have witnessed; *the superfluous blood soon disappears.* How this occurs is still obscure, owing to the want of adequate investigation; for even if the opinion held by many be correct, and the disintegration and solution of the superfluous blood-corpuscles is really evidenced by the icterus neonatorum, this alone would supply no information as to the fate of the transfused blood as a whole. Probably the disintegration and removal of the superfluous blood takes place in the new-born in essentially the same way as in full-grown animals; in that first the plasma and afterwards the corpuscular elements are disposed of. To me, at least, this view seems to be favoured by the circumstance, testified to by various older and more modern writers,* that the blood of children is soon after birth considerably richer in red blood-corpuscles than is the case some weeks subsequently.

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* Schücking, 'Berl. klin. Wochenschr.,' 1877, Nos. 1 and 2.

† Illing, 'Ueber d. Einfluss d. Nachgeburtsperioden anf d. kindliche Blutmenge,' I.-D. Kiel, 1877; Zweifel, 'Ctbl. f. Gynäkologie,' 1878, No. 1; Hofmeier, ibid., No. 18; Porak, 'Revue mens. de méd. et de chir.,' 1878, pp. 334, 429. Numerous references are contained in a dissertation, which abounds in naïveté, by Violet, 'Virch. A.,' lxxx, p. 353.

While, accordingly, the subject of plethora can claim no more than an essentially theoretical interest, it is otherwise with the *diminution of the blood-quantum, oligæmia*, or as it is commonly termed, *anæmia*. For every hæmorrhage must necessarily lessen the total blood circulating in the body, and this in proportion to its abundance. The effects on the circulation of such diminution of the blood-quantum have repeatedly been determined by observation of the human subject, and by experiments on animals. Everything depends, I need hardly say, on the *degree* of anæmia, *i. e.* on how large a fraction of the total blood has been lost by the hæmorrhage. A loss of one, or a few parts, per thousand cannot exert any effect worth mentioning on the circulation; for such variations in amount are fully within the physiological limits. But even where much more considerable degrees of acute anæmia have to be remedied, the physiological regulative mechanism of the organism is quite equal to the task. If you open an artery or vein in a dog and draw off a quantity of blood equal to 1 per cent. its body-weight, or about an eighth part its total blood, you observe during the operation a fall of arterial pressure, and the pulse becomes small and easily compressible. This, however, does not last long; after waiting about half a minute, the pulse gets more forcible under your finger, the mercurial column of the manometer ascends, and the carotid-pressure very soon regains its former level. Moreover, you may soon follow up the first phlebotomy with a second and really considerable one, say ½ per cent. the body-weight; and again the arterial pressure is observed to fall, and then to rise rapidly, precisely as it did before. The loss of even *more than a fourth part of the total blood* can be borne by many dogs, cats, and rabbits *without any lasting fall in*

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* Panum, 'Virch. A.,' xxix, p. 481; Hayem, 'Compt. rend.,' lxxxiv, No. 21, 1877.

their arterial pressure. It is obvious that this restoration to the original elevation cannot be effected in such a short time, reckoned as it is by seconds, by a refilling of the empty vessels; the regulation is effected by the *adaptation* of the arteries to the reduced blood-quantum, and above all by the intervention of the *vaso-motor nervous system*, by whose agency the regulation is brought about. Anæmia is an exciter of the vaso-motor centre; and acts more vigorously in proportion to its degree and rate of development. So soon therefore as, owing to the hæmorrhage, an abnormally small supply of blood is conveyed by the arteries to the medulla oblongata, the muscular coat of the vessels is excited to stronger contraction throughout the whole of the systemic arteries, as far as the vaso-motor centre rules; and in this way the pressure is restored. Henceforth the velocity of the flow is normal, and the frequency of the heart-beats as before the operation. But while a direct impairment of the circulation is prevented by this regulative mechanism, the latter cannot obviate all the disadvantages to the organism which a diminution in the blood-quantum must involve. For the amount of blood normally contained in the vascular system is so nicely adjusted to the needs of the body that the vigorous and ample stream required for the work of the individual organs can only be obtained by the simultaneous reduction of the blood-supply of other organs to a certain minimum amount. Now, when a quantity such as that mentioned above is lost, and the total amount of blood is reduced to five sixths or even three fourths the normal, whence can the blood be taken for the working organs without at the same time so impoverishing the remaining ones as to seriously threaten their integrity and physiological constitution? The occurrence of an anæmia in which the arterial pressure, and with it the velocity of the blood-stream and frequency of the pulse, at first remains quite unaltered is, you will observe, an event of no little moment. There can be no doubt that it would very soon be attended by highly injurious consequences were not the loss of blood compensated by a corresponding *regeneration*.

That such a regeneration actually ensues, and that even a considerable loss of blood is usually made good in from three to four weeks at farthest, is a fact established by thousands of observations, collected during the experience of centuries. But however indubitable the fact, we are still far from any knowledge of the *modus* of this regeneration, and of the processes by which it is brought about. The replacement of the water and salts may, it is true, be rapidly effected from the food; and when the apparatus of digestion and absorption perform their functions normally, not more than a few days will elapse before the albumen of the blood-serum is again normal in amount. The blood has then the same volume as before the loss, but it is poor in blood-corpuscles; the *oligæmia* has become an *oligocythæmia*. The disprotion concerns chiefly the red blood-corpuscles, for, as already noticed, the loss of colourless cells in hæmorrhage is always *relatively* smaller than is the loss of red ones; and, again, the lymph entering the blood is such an inexhaustible source of colourless corpuscles that the latter are never greatly diminished as the result of hæmorrhage; in any case the decrease is very quickly repaired. It is rather a condition of relative *leucocythæmia* that is developed after every somewhat considerable loss of blood, and this only gradually disappears as the normal quantitative relations between red and colourless blood-corpuscles are re-established. This implies that the replacement of the lost red corpuscles occurs much *more slowly* than does that of the colourless cells—a circumstance which partly explains how the details of the regeneration of the red blood-corpuscles have been so far enveloped in obscurity, but does not render this deficiency in our knowledge any the less palpable. Unfortunately, the veil which hides the life-history of the formed elements of the blood has up to the present been raised only in a few places, and physiology and pathology have both equally to complain that on this subject we are often left groping in the dark. True, there is no lack of hypotheses. The commonest view probably was till quite lately—that colourless blood-corpuscles are constantly being produced in certain organs, the lymphatic glands, the spleen, and perhaps the medulla of bone and the liver; that a number of these are being every moment transformed into red corpuscles; and that the latter are consumed to a corresponding extent in subservience to the ends of the organism. But when the entire question was subjected to a more acute and unbiassed criticism, it soon appeared that this doctrine is far from being based on indisputable facts. With regard to the spleen, Neumann,[*] one of our ablest writers in this department, recently failed to convince himself that more colourless corpuscles leave the organ by the splenic vein than are conveyed to it by the splenic artery; while, if the increase is merely relative, it might obviously be referred no less reasonably to a destruction of red corpuscles within the spleen. Bizozzero's observation[†] that winter frogs, whose bone-marrow is rich in fat, have much fewer colourless corpuscles in the blood than have summer-frogs with a marrow composed almost exclusively of lymphoid cells, does not, in my opinion, force us to conclude that the medulla of bone is the seat of a physiological production of colourless blood-cells; although the remarkable abundance of leucocytes in the veins leaving the femur in the latter species[‡] is clearly in favour of this view. And, lastly, with respect to the *lymphatic glands*, the question has been raised, to some extent justifiably, whether a considerable proportion of the lymph-cells leaving the gland by the v. efferentia are not colourless corpuscles which have emigrated from the blood-stream within the gland substance? As to the ultimate origin of the lymph-cells found in the lymphatics before the latter have passed the glands we are equally in the dark. Our knowledge of the physiological *consumption of red blood-corpuscles* is hardly less indefinite. No doubt a number of them are constantly being used up in the *production of bile*; and it is equally certain that the *urinary pigment* is a derivative of the colouring matter of the blood, and is therefore ultimately referable to the disintegration of red blood-corpuscles. Further, since the time when the discovery in the spleen and bone-marrow of cells containing blood-corpuscles had lent probability to the hypothesis that red blood-corpuscles are destroyed in both these localities, the notion has received much stronger support through the observations of

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[*] Neumann, 'Arch. d. Heilkunde,' xv, p. 441.

[†] Bizozzero, "Sulla funzione ematopoetica del midollo delle ossa," 'Gaz. med. ital.-lomb.,' Nov. 1868.

[‡] Neumann, 'Arch. d. Heilkunde,' x, p. 68; 'Berl. klin. Wochenschr.,' 1878, No. 6 and following.

Quincke.* This writer showed how blood-corpuscles are transformed in the spleen, bone-marrow, and hepatic capillaries into iron-albuminates, which are in part yellow coloured and in part colourless, and may be detected micro-chemically in granular form or in solution. But to what extent, and under what conditions, this transformation takes place we have no information; nor do we know whether a destruction of red corpuscles takes place in other organs as well, or in the circulating blood itself. What, then, can be said of the *intermediate steps*, the transformation of white blood-cells into red? Which of the colourless corpuscles experience the metamorphosis, and where, in which organs, does it occur? Whence is the hæmoglobin derived? What becomes of the nuclei of the colourless cells and what of their granules? We are met by a multitude of questions which are still completely unanswered. Positive observation of the transformation of a colourless blood-cell into a coloured one is mainly confined to a very short communication by Recklinghausen,† who states that if frog's blood be kept in carefully cleaned glass vessels from which the air is not excluded, certain spindle-shaped colourless cells acquire the colour of the red corpuscles in from eleven to twenty-one days. Unfortunately, this preliminary communication has not been followed, during the fifteen years which have since elapsed, by a more detailed one, so that any criticism as to how far the methods and results admit of such an inference, is at present impossible. The statements of other writers refer chiefly to mammalian blood. Erb‡ looks upon *granular* coloured cells as transitional forms. He has found great numbers of these in the blood after hæmorrhage, and he explains the entire process by supposing that the colourless cells first lose their nuclei by disintegration and solution, then take up hæmoglobin, and afterwards become transformed into homogeneous discs. Al. Schmidt,§ on the other hand, lays special stress on certain large, protoplasmic, nucleated cells *with red coarse*

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* Quincke, 'Festschrift zum Andenken an Alb. v. Haller,' Bern, 1877, p. 37; 'D. A. f. klin. Med.,' xxv, p. 567, xxvii, p. 193.

† v. Recklinghausen, 'Arch. f. mikrosk. Anatomie,' ii, p. 137.

‡ Erb, 'Virch. A.,' xxxiv, p. 138.

§ Al. Schmidt, 'Pflüg. A.,' xi, p. 515.

granules, which, he says, are always present in normal mammalian blood, and which, when outside the vessels, rapidly lose their colour, and are thus changed into *colourless granular corpuscles*. He regards these forms as the analogues of the permanent red blood-cells in the three lowest vertebrate classes, and supposes that the non-nucleated red blood-discs of mammals are produced by the blending of the coarse red granules with the nucleus, while the remainder of the protoplasm dissolves and disappears. But perhaps the chief interest of the whole question centres at present in the *nucleated red blood-corpuscles*. These were long ago recognised in embryonic blood, have occasionally been observed in the blood of leucæmic adults,[*] and were shown by Neumann[†] to be always present in the red marrow of bones, though most abundantly so in early life. For, according to Neumann, these red nucleated cells are *transitional forms* between the colourless and the red non-nucleated corpuscles; hence he inferred that new colourless cells are constantly produced in the bone-marrow, that these penetrate the very wide and extremely thin-walled, perhaps wall-less, capillaries of the medulla, and are transformed in their interior into red nucleated, and further into non-nucleated blood-corpuscles.

By formulating the hypothesis in this way two things, not necessarily connected, have been brought into conjunction. For granted that the red nucleated corpuscles are the antecedents of the non-nucleated ones, it by no means follows that the former have originated in a metamorphosis of colourless cells, or represent the desired transitional form between the latter and the non-nucleated red corpuscles. There are, indeed, a number of weighty facts which tell in favour of the nucleated blood-cell being a developmental form, an antecedent stage, of the non-nucleated one. Thus, it has long been known that the embryonic blood of mammals at first contains only nucleated red blood-corpuscles, the non-nucleated variety appearing subsequently. Further, there is complete unanimity amongst all observers that, in circumstances where there is reason to assume an increased production of blood-corpuscles, the number of nucleated red cells in the bone-marrow, the spleen,* and even in the blood† is considerably augmented. Lastly, Rindfleisch‡ states that he has directly observed in the embryo of the guinea-pig how the nucleated red blood-cells, called by him hæmatoblasts, extrude their nuclei, which then persist as colourless corpuscles having a small amount of protoplasm, while the cells themselves develop into non-nucleated blood-corpuscles, at first bell-shaped, later on acquiring the ordinary discoidal form, and only to be distinguished from the fully matured corpuscles by their somewhat smaller size. As you will readily see, this observation of Rindfleisch is more convincing than all the other reasons adduced; and it would therefore be very desirable that his statements should soon be confirmed on all hands. The results arrived at in the embryos of guinea-pigs as to the fate of the nucleated red cells might certainly be applied without hesitation to the same structures occurring in adults.

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[*] Klebs, 'Virch. A.,' xxxviii, p. 190; Böttcher, ibid., xxxvi, p. 364; Eberth, ibid., xliii, p. 8.

[†] Neumann, 'Arch. d. Heilk,' x, p. 68, xi, p. 1; Bizozzero, 'Sol midollo delle ossa,' Napoli, 1869.

In support of the second point, the origin of the nucleated red cells from colourless ones, equally satisfactory evidence is assuredly not forthcoming. For the mere fact that the development of the colourless corpuscles in the embryo occurs prior to the appearance of the nucleated red ones cannot be brought forward in support of this theory, since the formation of nucleated red blood-cells takes place quite independently of the colourless corpuscles already present. Nor, so far as I can judge, has actual proof of the truth of their view been brought forward as yet by any of the writers, *e. g.* Rindfleisch, who believe in the transformation of colourless blood-cells into red nucleated corpuscles. It is not surprising therefore that the adherents of the doctrine have sensibly diminished during the last few years. Neumann§ himself soon began to doubt whether the nucleated red cells should be regarded as "transitional forms," and he now considers it more advisable to term them simply *embryonic* or *developmental forms*. Moreover, if Bizozzero[*] has succeeded, as he states, in convincing himself, even when employing modern criteria, of the correctness of the view advanced by him years ago, according to which the multiplication of the red nucleated corpuscles takes place by division, we must agree with him that the hypothesis of a transformation of colourless into coloured corpuscles has become superfluous. A great deal of further investigation is necessary before we can determine the conditions, and especially the whereabouts, of the new formation of nucleated cells, and of the transformation of these into non-nucleated corpuscles. It would best harmonise with our ideas of the functions of our organism were we to seek the seat of these processes, not in the circulating blood itself, but in certain organs, in the first place in the bone-marrow, and then perhaps in the liver and spleen.

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* Bizozzero, 'Med. Ctbl.,' 1879, No. 16.

† Ehrlich, Lecture in the "Gesellschaft der Charité-Aerzte" in Berlin of 10th June, 1880; 'Berl. klin. Wochenschrift,' 1880, No. 28.

‡ Rindfleisch, 'Arch. f. mikrosk. Anat.,' xvii, pp. 1, 21.

§ Neumann, 'Arch. f. mikrosk. Anat.,' xii, p. 792.

Lest you should have got the impression from anything I have said that this highly important question has already been established on a secure and generally accepted foundation I may mention, in conclusion, the opinion of a much-quoted French writer,[†] who supposes the antecedent stage of the red blood-corpuscles to consist in very small, unstable, and perishable coloured corpuscles, found sparingly by him in normal blood, but very abundantly in anæmic conditions. We shall again meet with these *microcytes* in so-called essential anæmias; and I shall then have to tell you that the majority of writers look upon them as products of the disintegration of typical red blood-corpuscles. It is, however, very characteristic of the present state of the entire question that it should be possible for the same appearances to be interpreted by circumspect and distinguished investigators in directly opposite senses.

So long as our knowledge of the physiological regeneration of the blood remains in this unfortunate state, you cannot expect a satisfactory explanation of the processes by which the replacement of the red blood-corpuscles is effected after hæmorrhage. There is no evident reason for assuming *a priori* that this replacement occurs otherwise than in physiological regeneration, and it is for this reason that the condition of the blood and of the blood-producing organs subsequent to hæmorrhage has been with many writers the starting-point and basis of their investigations into the new formation of the blood-corpuscles. Yet it is not impossible that this circumstance has directly prejudiced the results of the researches in question. It may reasonably be asked whether the truth of the assumption involved, *i. e. an abnormally increased formation of red blood-corpuscles after bleeding*, is really established beyond all doubt. Of course I do not mean to dispute the increase of the blood in volume soon after the hæmorrhage has ceased; this would be no more than happens in other tissues which have been reduced by inanition, where on the removal of the cause a corresponding replacement ensues; nevertheless this "accelerated repair" need not include the red blood-corpuscles. Moreover, however apposite may appear the remark of Neumann* that, owing to the rigidity of the walls of the medullary cavities, very little blood can escape during hæmorrhage from the vessels of the medulla, yet the most to be inferred therefrom is that the conditions on which the regenerative activity of the medulla depends are not substantially worse after hæmorrhage than under normal circumstances; it affords no evidence for a possible *increased* production of colourless or of nucleated red corpuscles. I need hardly say that it is not permissible to adopt a line of argument like the following, and to conclude that the organism simply produces more blood-corpuscles in order to make good the loss, *i. e. because* in a given space of time a greater number of corpuscles have perished than should normally be the case. An assumption of this kind is without support till it can be shown that, owing to the hæmorrhage, new conditions are created, leading up to and causing an abnormally large production of blood-corpuscles. Now, bearing in mind the extraordinary adaptation of the animal organism to its ends, it cannot be denied that the existence of these conditions is highly probable; do not, however, be led into supposing that there is any scientific proof of it as yet. But, in my opinion, the assumption that the production of blood-corpuscles is abnormally increased after a loss of blood may be dispensed with. From his estimations of hæmoglobin, and the micro-chemical reactions of the spleen and liver in artificial plethora, Quincke calculates the mean duration of life of the red blood-corpuscles to be something more than two to three weeks. If true, this involves the capacity on the part of the organism of reproducing physiologically in about three weeks the whole amount of red blood-corpuscles present in the vascular system at any time. This is a feat, however, which would more than meet the case of the severest hæmorrhage. To me, at least, a gradual replacement of the lost blood-corpuscles without any call upon an abnormally increased production appears quite comprehensible, if it be assumed that the *consumption of red blood-corpuscles is diminished in the interval following a loss of blood*, so long as any deficiency of blood-corpuscles remains. This assumption would completely harmonise with the fact that the performance of all those functions in which blood-corpuscles are probably used up is feebler after hæmorrhage; and is exemplified more particularly by the secretion of a faintly coloured bile and pale urine by anæmic or hydræmic individuals. Of course I do not at all mean to *assert* that the restoration of the blood-corpuscles after hæmorrhage is due solely to a falling-off in their consumption. On the contrary, you will not, I hope, understand my statements as indicating anything but a desire to emphasize the inadequacy of our information on the regeneration of the blood after hæmorrhage, as well as to point to possible sources of error which may have crept into many of the researches dealing with this topic.

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[*] Bizozzero, 'Med. Ctbl.,' 1881, p. 129.

[†] Hayem, 'Recherches sur l'anat. norm. et path. du sang,' Paris, 1878; 'Arch. de physiol. norm. et path.,' 1878, p. 692; 'Gaz. méd.,' 1878, p. [illegible] 'Compt. rend.,' lxxxiv, p. 1239, 1877.

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* Neumann, 'Arch. d. Heilk.,' x, p. 68, xi, p. 1.

But however the regeneration of the blood-corpuscles may be carried out, with its completion the last after-effects of the anæmia are removed, and accordingly a loss which does not exceed the limits mentioned causes no disturbance of the circulation whatever. Not so when the hæmorrhage has passed these limits. I have already told you that the loss of about half the total amount of blood is fatal as a rule. Let us now see what effect is exerted on the circulation by the withdrawal from the vascular system of more than quarter, and less than half, the contained blood. After such a loss the arterial pressure does not reascend but continues low, and that in proportion as the anæmia approaches the fatal limit. A lasting fall of arterial pressure must evidently be accompanied by slowing of the blood-stream, so that, *e. g.* if the blood-letting be continued, the time necessary to obtain a certain quantity from the artery gradually increases. As regards the cardiac pulse-rate, the imperfect filling of the ventricle is *per se* a cause of retardation; but commonly the circumstance that the vagus centre is more feebly excited by the lowered arterial pressure tells in an opposite direction, and the pulse is wont to be even accelerated. The lessening of the distance between the summit and hollow of the wave in the arterial curve is also very striking; in other words, the single pulsations are much smaller than before the hæmorrhage, in correspondence with the reduction in the total quantity of blood, and the associated imperfect filling of the heart during diastole.

But although the lowering of pressure and slowing of the blood-stream which follow a loss of blood of from 2½ to 3 per cent. the body-weight continue pretty long unaltered, the *constitution* and *quality* of the blood undergo some remarkable changes. So soon, namely, as the blood-pressure has fallen to a low level—and values of from 40 to 50 mm. mercury are not uncommon in the carotid of a strong dog from whom a good third of the total blood has been taken—the osmosis through the walls of the capillaries is reversed, and for the transudation in an outward direction there is substituted a diffusion and resorption *from without inwards*. At the same time the lymph-stream flows at an increased rate from the ductus thoracicus into the empty vena subclavia. But even in the absence of the latter factor the blood would become more watery after such a hæmorrhage. Lesser* has shown directly that when the ductus thoracicus is ligatured in blood-letting the water contained in the serum steadily *increases*. The increase can therefore depend only on a resorption of the fluids of the parenchyma. But the red bloodscles, and therewith the colour-intensity of the blood,

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sser, 'Ber. d. Leipz. Ges. Math.-Phys. Kl.,' 1874, p. 153.

decrease to a relatively greater extent than the watery contents of the serum increase; apparently because the specifically heavier red blood-corpuscles escape from the opened artery in larger numbers than would correspond to their proportions in the circulating blood. This dilution of the blood by resorption of the fluids will terminate only when a state of equilibrium between the pressure in the capillaries and the pressure of the surrounding fluids is re-established. But the arterial pressure is then still far from having recovered its former elevation; for this it is necessary to resort to very different measures, of which the most certain and effective is *the transfusion of blood from an animal of the same species.*

The incomparable superiority of transfusion, as compared with all other remedies employed in hæmorrhage, may be briefly defined to consist *in the restoration by its means to the body of the lost material in the most direct and perfect manner.* For the blood transferred to the depleted vascular system, if it retains its vital properties, at once becomes an integral part of the new organism. Hence it is best to take it fresh from one of the veins of an individual of the same species. All the transfused blood-corpuscles continue perfectly intact, and participate, just as do those already present, in the respiratory exchange of gases; and similarly the transfused liquor sanguinis is employed in lymph-production and transudation. It is quite immaterial whether ordinary or defibrinated blood be introduced; for a serious impoverishment in colourless corpuscles can hardly ever arise in hæmorrhage. Of course in defibrinating we must employ a method by which as little fibrin-ferment as possible is set free; we must never make use of blood expressed from a clot, but only of that taken from a vein and whipped or agitated in the usual way, by which means blood of very slight fermentative energy is obtained. Much more important than the choice between ordinary and defibrinated blood is the employment of blood taken *from an animal of the same species.* For then only does the tranfused blood live and perform its functions in the foreign vascular system; while blood *from a different species* is not merely useless, but *may even prove most pernicious to the recipient.* That the transfer of such blood, *e.g.* from a lamb to a fox, or from a sheep to a dog, is injurious and determined more than two centuries ago by very good observers.[*] Nevertheless, a therapeutic mystification of recent years, not very flattering to medical science, was needed to bring the interesting question of the relations and action of foreign blood in the vascular system to the test of experiment.[†] It was then found that the injection of comparatively small amounts—as a rule, not more than 20 per cent. the original blood-quantum—led to the animal's *death*, which generally took place as early as the first or second day. Most of these experiments have been carried out by introducing lamb's blood into dogs; and it is to this combination that the above-mentioned figures apply. But even the dogs which survived the injection of lamb's blood, owing to the amount introduced being less than 10 per cent. their blood-quantum, showed symptoms of severe illness during the days immediately following the operation. Hæmatemesis and diarrhœa, dyspnœa, loss of appetite, and great feebleness were seen in all cases where the amount transfused was not altogether too small; and one very remarkable sequela in particular was never absent, namely, the *tendency to hæmorrhage*. This tendency manifested itself both by actual *extravasations* into some of the organs and serous cavities, as well as by mere *bloody staining*, that is, by admixture of the *blood-pigment, hæmoglobin*, with the transudations, *e.g.* the aqueous humour, and the urine. As regards the *hæmoglobinuria* Ponfick has brought forward proof of its invariable occurrence on the introduction of more than 1 per cent. of foreign blood into the vascular system of a dog. The dangerous effects of blood of another species on the circulation and condition of the animal are undoubtedly attributable in part to the fact *that the blood-serum of one species is a poison for the blood-corpuscles of another.* This remarkable fact was first determined by Prévost and Dumas, and has recently been more accurately defined by Landois to consist in the direct *solution* of the blood-corpuscles of some species by the serum, as well as by the lymph and transudations of others.* It is not that the mixture of the blood of two species is followed by the solution of all the corpuscles of each, but that the different species have corpuscles *of unequal resisting power*; the blood-corpuscles of the rabbit are dissolved in the blood or serum of the dog, but the corpuscles of the dog resist the action of rabbit's blood. In a solution of blood-corpuscles, whether of the transfused corpuscles or of those belonging to the animal, the hæmoglobinuria and staining of some of the transudations with blood-pigment undoubtedly originate. Yet the various other severe symptoms are not so easily accounted for. With respect to the hæmorrhages, I may remind you of what I recently stated (p. 396) of a possible connection between them and the dearth of functional red blood-corpuscles; but it is also possible that the *free hæmoglobin*, or the foreign blood, may exert a directly destructive influence on the vessel walls. Here too, as in so many other cases, it is not known whether the bleeding occurs *per diapedesin* or *per rhexin*. Whether the foreign blood impairs the function and condition of the individual organs, and if so how far, also requires further investigation. In particular, the suggestion thrown out by the Dorpat School that fibrin is set free by the injection of blood of another species deserves the fullest consideration, although in my experience extensive coagulation is not a usual result of this operation.

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[*] Quotations by Scheel, 'Die Transfusion des Blutes u. d. Einspritzen d. Arzeneien in die Adern,' continued by Dieffenbach, Berlin, 1828.

[†] Prévost and Dumas, 'Ann. d. chim.,' 1821, xviii, p. 294; Panum, 'Virch. A.,' xxvii, pp. 240, 433, lxiii, p. 1, lxvi, p. 26; Brown-Séquard, 'Compt. rend.,' 1851, 1855, 1857; 'Journ. d. phys.,' i, p. 95; Landois, 'Med. Ctbl.,' 1873, Nos. 56, 57; 'Die Transfusion d. Blutes,' 1875; Ponfick, 'Berl. klin. Wochenschr.,' 1874, No. 18; 'Virch. A.,' lxii, p. 273; Worm Müller, 'Transfusion u. Plethora,' 1875.

This being the state of affairs, it would appear not merely useless, but absolutely reprehensible, to employ any blood but that of the same species, where an indication for transfusion exists. Among these indications anæmia brought on by loss of blood ranks first, for reasons already stated. In the second place, transfusion seems to be indicated when the object is to replace blood which through any cause has become functionally incapable by blood which is normal and functionally capable. Clearly the latter indication is invalid except where the cause of the ruin and loss of function of the blood has been removed, or is capable of removal, as *e. g.* in carbonic oxide poisoning. I cannot look upon it as rational to replace (or, as it is technically expressed, *substitute*) the blood of a diabetic, leucæmic, pyæmic, or even tuberculous person by foreign blood from a healthy individual. But where the substitution is really indicated, the transfusion of healthy must of course be preceded by the removal of the useless blood ; and success is assuredly more rapid and permanent in proportion to the amount exchanged. The extent to which this may be carried you can estimate from the success of Panum,[*] who replaced almost the entire blood-quantum of a dog by blood obtained from another, without any disturbance in the condition or functions of the animal.

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* H. Cordua, 'Ueber d. Resorptions-Mechanismus b. Blutergüssen,' Berlin, 1877.

There are many ways of introducing the new blood into the vascular system.[†] The simplest appears to be direct conduction from an artery of the donor into a vein of the recipient. Nevertheless this procedure, which in the human subject is clearly for various reasons a doubtful one, cannot in my opinion be recommended even for animals. For to say nothing of the absolute impossibility of determining during the operation the amount of blood transfused, the method is attended by an unavoidable evil in that the new blood flows *under high arterial pressure* into the veins and right heart of the recipient—an occurrence which may occasionally be followed by the most serious consequences to the heart, more especially in highly anæmic individuals and in cases of poisoning. This too is my reason for warning you against the employment of a syringe in injecting the blood into a vein ; at any rate it is safer to allow the blood, which of course has previously been whipped, filtered, and warmed, to run from a funnel through a cannula of glass. Yet if I may venture to form an opinion from my experience with animals, even this method cannot be regarded as altogether innocent or safe ; not only because it is sometimes found impossible, despite the greatest care, to prevent the entrance of air-bubbles or of small clots formed subsequently to filtration, but because, as I have repeatedly observed, the entrance of an abundant blood-stream under a pressure of not more than 10 to 12 mm., mercury exerts upon the anæmic and enfeebled heart a paralysing rather than a vitalising influence. All such dangers may be avoided with the greatest certainty by introducing the new blood into the *arteries* instead of the veins. True, one should not under any circumstances venture to inject into the peripheral end of the divided artery; for the peripheral ramifications contract against the foreign blood with so much energy that powerful efforts are called for to overcome the resistance, and it is rare to escape without bursting the vessels. Not so when the central end is chosen, and the injection carried out by means of a syringe, under a pressure barely sufficient to overcome the arterial pressure prevailing at the spot. The blood at once mingles with that contained in the central portion of the artery, flows without any resistance through the lateral branch next above into the arterial and capillary ramifications, and thence under perfectly normal venous pressure to the heart. According to my experience, which it is true extends only to animals, I can pronounce *central arterial transfusion* to be the least dangerous, and at the same time a perfectly effectual procedure. At all events I fail to perceive any special advance, as compared with direct injection into the vascular system, in the method of *indirect transfusion from the peritoneum,* which has recently been recommended, more especially by Ponfick.* It is true that, as I mentioned lately (p. 406), a considerable quantity of blood can be absorbed by the peritoneum, and in a comparatively short interval. Yet a good deal more time is always consumed than is needed for direct injection; and this alone is reason sufficient for dispensing with peritoneal transfusion in those cases in which the direct method has achieved its greatest triumphs, namely in anæmias where the danger is immediate: at most in the slighter degrees of anæmia can it rival the direct method. But in man, the operation of introducing a cannula into the peritoneal cavity is certainly no easier than is the finding of a superficial vein or artery; and it is decidedly more dangerous. For to say nothing of other mishaps, perfect disinfection of the blood to be introduced is quite impossible; and it is obvious that much greater risk attends the introduction of impurities into the abdominal cavity than into the vascular system. In fact I know already of several cases where a fatal peritonitis set in after peritoneal transfusion, although performed by some of the best and most painstaking operators. And should it be objected that the operation has in a large number of cases been attended with good results, it would not be the first occasion in the history of transfusion on which proof has been afforded of how much a human being can endure; and again consider for a moment in what consists the claim of a transfusion to "good results." Actually demonstrative of the remedial effect of transfusion are, it is evident, only those cases in which the patient has survived a loss of blood which, but for the operation, would have proved fatal; a loss, that is, of about half the blood-quantum. In all anæmias of slighter degree, the fact that the patient may spontaneously recover leaves it more or less to the subjective inclination of the physician whether or not he will credit the transfusion with an important share in the result; in making which statement I take no account of those instances where transfusion* has been carried out to meet perfectly irrational indications.

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[*] Panum, 'Virch. A.,' xxvii, pp. 240, 433.

[†] Cf. L. v. Lesser, 'Die chirurgischen Hilfsleistungen bei dringender Gefahr,' Leipsig, 1880, p. 49 ; 'Volkmann'sche Vortr.,' No. 86 ; Jürg-Ziemssen's 'Hdb. d. allg. Therapie,' i, 2, p. 240.

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* Ponfick, 'Bresl. ärztl. Zeitschr.,' 1879, No. 16; cf. also Foà e Pallacani. 'Studi sulla fisiopatologia del sangue e dei vasi sanguigni,' Modena, 1880

In order that the bad effects of a severe hæmorrhage may be fully neutralised by a direct transfusion of new blood, it is clearly necessary to introduce a quantity equal, or nearly equal, to the loss. On doing so, it is indeed one of the most pleasing spectacles to observe how rapidly and perfectly the recovery of an animal, which had been reduced by severe hæmorrhage to a condition of extreme anæmia, ensues. The individual pulsations very soon become larger, while the arterial pressure rises in exact proportion to the amount of blood introduced, till it has reached about the normal value. If the dog be now removed from the operation-table he begins at once as a rule to run about, brisk and strong—the same dog, which before was too weak to lift his leg a little. *And the recovery* is, as has more than once been stated, *a permanent one*. Now it is easier to make than to meet the demand that as much blood as has been lost shall be introduced into a patient after a dangerous hæmorrhage; for where is three or four pounds of fresh, whipped, human blood to be obtained? We must usually be satisfied with less, and though we certainly improve the situation of the anæmic individual, we cannot at once restore him to the state he was in before the occurrence of the hæmorrhage. His situation is improved, not merely because the severity of the anæmia has been reduced, but also because its duration is shortened by lightening the task of the blood-producing organs; it is as though a proportionately smaller loss had occurred instead of the larger one.

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* Cf. *e. g.* v. Kaczorowski, 'D. med. Wochenschr.,' 1880, No. 46.

In transfusion of blood from an animal of the same species we accordingly possess an ideal remedy for anæmia, a remedy unequalled by any other. Nay more, we may say that, except transfusion, no other direct remedy exists. Where transfusion is not called upon to aid, the normal blood-quantum can only be restored by the regenerative activity of the organism; in which case the efforts of the physician must be restricted to securing the most favorable conditions possible for this regeneration. Now our knowledge of these conditions, as you will readily believe, is far too imperfect to allow of our making it the basis of any special remedial measures; but however this may be, at all events one thing is necessary—that the individual should remain alive. The essential danger arising out of a severe loss of blood consists in the fall of the blood-pressure to such an extent that life cannot be sustained even for a short time. For this reason every means by which the blood-pressure can be raised in very anæmic individuals must be heartily welcome. Such a means, and a very simple one moreover, is the transfusion *of a weak solution of common salt.* The concentration to be chosen is that which is as far as possible indifferent for the blood-corpuscles of the species in question; in the dog it is 6 per 1000, and the solution may be rendered alkaline by the addition of caustic soda, ·05 to a litre of fluid.* The course of the experiment is usually most convincing. After having reduced the blood-pressure of a strong dog to half or even a third the normal by copious blood-letting, you allow a quantity of warmed salt-solution equal to the blood withdrawn from the animal to run into a vein; whereupon you will notice the pulsations immediately becoming larger, and the arterial pressure ascending to its original level, where, as I have repeatedly convinced myself, it remains unaltered for half an hour or more. How soon it again falls I am unable to inform you; but at least time is gained, and an opportunity afforded to the regenerative processes of asserting their influence. Possibly the high arterial tension is in itself directly advantageous to the latter. Kronecker and Sander, in a communication,* the aphoristic character of which has not, it is true, as yet been amplified, report that they have definitively saved dogs from inevitable death by injecting the alkaline solution of common salt; nevertheless we must wait in order to see in how far this termination can be regarded as the rule. Meanwhile, in man at least I should not venture to reckon on it with confidence. In cases where, owing to immediate danger to life, I had for want of healthy human blood made a tranfusion of salt solution, I should consider it advisable to follow this up as soon as possible by a transfusion of blood.

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* Kronecker u. Sander, 'Berlin. klin. Wochenschr.,' 1879, No. 52.

At all events, if the latter course be not adopted, we cannot properly speak any longer of simple anæmia; for the fluid now circulating in the vessels is not normal blood. A far smaller quantity of blood-corpuscles is apportioned to each unit of blood, and the chemical composition of the plasma is essentially altered; the saline matters and extractives may not greatly deviate from the normal, but the albuminous contents are certainly diminished; in a word, *such an individual is not anæmic but hydræmic.* The same thing applies, if possible, with still greater force to those extreme anæmias which are the result, not of *one severe hæmorrhage,* but of *smaller often-repeated losses of blood.* I have already dwelt on the fact that bleeding which does not lastingly influence the arterial pressure is invariably followed by a period, though of short duration, in which the composition of the blood is altered at the expense of the blood-corpuscles and of the dissolved albumen. Should a fresh bleeding occur during this period, before the regeneration is complete, the composition of the blood must of necessity be further impaired, and *hydræmia* will here be still sooner developed, *i. e.* before such a quantity is lost by the repeated bleedings as would be necessary for the *rapid* development of a hydræmia of equal severity, Still less would it be legitimate to place amongst the quantitative alterations—the anæmias *in specie*—those changes in the composition of the blood which result from defective nutrition, or from abnormal loss of the juices, as in profuse suppuration and albuminuria, or from the appropriation of certain constituents of the blood in the production of large tumours. For though the blood-quantum may in these cases be reduced, at all events the *composition* of the blood invariably shows an essential departure from the normal, and the latter is then to be taken as the criterion.

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* Kronecker u. Sander, l. c.

CHAPTER VIII.

HYDRÆMIA AND ANHYDRÆMIA.

Importance of the constitution of the blood for the circulation.—Hydræmic plethora, and simple hydræmia or hypalbuminosis.—Combination of both.—Causes of hydræmia.

Older theory of hydræmic dropsy.—Objections to it.—Experiments.—Effect of hydræmic plethora on blood-pressure and velocity, on secretions, and on the lymph-stream.—Localisation of dropsy.—Action of simple hydræmia on the circulation and transudation.—Inferences with respect to hydræmic œdemas.—Explanation of these.—Résumé.

Concentration of the blood and its effect on the circulation.

In discussing now the influence which qualitative changes in the blood exert on the circulation, only those alterations of composition that are of importance to the flow itself can properly be of interest to us. Whether an abnormal constituent of the blood is injurious to the nervous system, or affects the function of the kidneys, or of any other organ, is at present a very secondary matter; and we accordingly ask simply whether the heart and vessels, the circulation, or the transudation is influenced by the particular change in the quality of the blood. If these continue normal the alteration in the blood has no significance for the circulation, and is not included in the task we have set before us to-day. But in thus limiting our inquiry we have at the same time indicated the points which must be kept in view during its prosecution. Normal blood is a watery solution of certain substances, having a definite concentration, and holding sus- in it the corpuscular elements, red and colourless scles. The normal degree of concentration, in conjunction with the suspended corpuscles, secures precisely that amount of internal frictional resistance, chiefly in the capillaries, which may be looked on as functional in maintaining a regular circulation. This frictional resistance was neglected when we were dealing with the factors causing the difference of pressure between the arterial and venous systems, because it is always a constant value so long as the constitution of the blood is normal. It is possible, however, that it may not remain so when the blood becomes abnormal in composition, and we shall therefore have to consider in the first place,—how an *alteration of the frictional resistance in the capillaries*, dependent on a change in the quality of the blood, must affect the circulation. In the second place, the *transudation* through the vessel-walls must necessarily be influenced by an alteration in the composition of the blood, since the processes of filtration and diffusion give different results when the liquid on the filter, or on one side of the membrane, is altered. Possible changes in the *liquor sanguinis* have, therefore, to be considered; while alterations affecting the number or constitution of the blood-corpuscles are of importance only for the exchange of gases, to be discussed in another place. Thirdly, since it is the blood that nourishes the heart and vessels, and maintains their normal functional power, we shall have to discuss how far the *constitution and function of the heart and vessels* are influenced by changes in the composition of the blood. Now you will hardly expect me to give you in this connection an extract from the toxicology of cardiac and vascular poisons, especially as we have already dealt with the question of paralysis of the heart and vessels, on which the bulk of such cases depends. It appears to me better to restrict ourselves to those alterations in the composition of the blood which are observed as natural, though at the same time pathological, events. Fourthly and lastly, the red and colourless corpuscles are themselves dependent on the normal plasma as being the medium in which they may best preserve their integrity, and it will therefore be a question whether the *blood-corpuscles* are influenced and injured by an abnormally constituted plasma, and if so, to what extent.

These being the various standpoints from which we shall discuss the effects of qualitative changes of the blood on the circulation, there results a further, and in my opinion, perfectly natural, classification of the possible alterations into 1, those involving the *liquor sanguinis,* and 2, those affecting the *blood-corpuscles.* If the regularity of the circulation and transudation, if the integrity of the heart, the vessels, and the blood-corpuscles are dependent on a certain albuminous contents—a certain concentration—of the plasma, the question arises, in what way are all these influenced by a *thinning* or *dilution* of the blood? Yet when speaking of *hydræmia,* you will carefully distinguish between two different conditions. Blood is hydræmic both when the contained water is *absolutely* increased, and also when the increase is only *relative.* In the first case, the total amount of solid constituents in the blood—that is, chiefly the albumen—remains *unaltered,* while, in the second case, it is *diminished.* On the other hand, the total weight and *volume of the water of the blood is normal* in the latter case, while in the former it is abnormally *increased.* But a third possibility is *a priori* admissible, namely that the albumen contained in the blood is diminished, while the total amount of water is increased; this combination must indeed cause an especially severe degree of hydræmia. Let us first examine which of these forms come under observation pathologically, and in what conditions this occurs.

That, in a normal state, the watery contents of the blood remain approximately constant, is the result, you are aware, of the excretion by the kidneys, skin, and lungs of a quantity of water exactly equal to that taken up by the blood; and conversely. It is on the kidneys that this regulative function is chiefly incumbent, more especially in animals which do not sweat, and therefore lose but a small amount of water by the skin. But in man also, it is only occasionally, as in midsummer, that the skin takes a prominent part in regulating the watery contents of the blood, while ordinarily the most important share is borne by the kidneys. Since we are constantly supplying the blood with water from our food, its watery contents must necessarily undergo an absolute increase as soon as the excretion by the organs concerned, and espe- by the kidneys, is *hindered.* The pathological processes which most commonly cause the excretion of water by the kidneys to be impeded and diminished cannot be thoroughly discussed till we come to deal with the pathology of the urinary secretion. At present I must content myself with referring to a few of the principal points. In the first place, all those processes which, involving both kidneys, impede the access of the blood to the glomeruli, have to be considered here; for the glomeruli are the portions of the renal vascular system by which the water is separated from the blood. The classical example of such a process is presented by *granular atrophy*, in consequence of which many of the glomeruli are directly destroyed, the blood-supply of other obstructed, and at the same time numerous uriniferous tubules rendered impervious. Then we have the diffuse double *nephritis*; for you know that the arteries and capillaries of an inflamed organ oppose an abnormal resistance to the blood-stream. In the case of the kidneys, however, this circumstance is of more far-reaching importance than elsewhere, inasmuch as the secretion of urine depends on the *blood-pressure* in the glomeruli, and *not on the quantity* of blood present in them. For from this it follows that the lowering of pressure in the glomeruli, inseparable from every nephritis, must cause the amount of urine to be reduced. Lastly, abnormal resistances situated in the *urinary passages* will greatly disturb and diminish the secretion of urine. Any impediment in the ureters which is not overcome by the pressure of the urine very quickly puts an end to further secretion by the kidneys. If such resistances are seated on *both sides*, the resulting decrease may be very considerable. To some of the above-mentioned affections there is added, from causes which I shall afterwards more thoroughly explain, an hypertrophy of the left ventricle, under the influence of which the arterial pressure is lastingly elevated. When this occurs, there takes place such an augmentation of the secretion from the glomeruli still remaining pervious that the influences tending to reduce the urine are fully neutralised, or even more than neutralised. But an adequate degree of cardiac hypertrophy is not developed in all cases of granular atrophy; and in the other diseases above mentioned, it is by no means an invariable occurrence. Moreover, the most extreme hypertrophy of the heart could not do away with an obstruction of the ureters due to impacted calculi. In these circumstances an amount of water equal to that by which the urinary secretion is reduced remains in the blood; and since there is no falling-off in any of the other constituents of the latter the volume of the blood must evidently increase—there arises a *plethora;* not a simple, but an *hydræmic* one. It is more than doubtful whether such an hydræmic plethora can ever be caused by diseases of the skin, and its production by pulmonary disease is still less likely. An overloading of the blood with water could hardly result from such affections, so long at least as the kidneys perform their functions normally.

Still more common than hydræmic plethora is simple *hydræmia,* which is produced by a deficiency of the solid constituents of the blood. Hæmorrhage, whether taking the form of a single large, or of small, often-repeated, bleedings, was lately referred to as one of its causes; and I then laid stress on the fact that the latter more readily lead to an hydræmic quality of the blood. But in order to give rise to hydræmia it is not at all necessary for actual blood to be lost by passing directly out of the vessels; *everything that consumes the albumen of the blood* must, in the absence of a corresponding repair from the food, necessarily lead to a relative increase of the watery contents. For the albumen so greatly preponderates over the other solid constituents of the blood-serum, that the salts and extractive matters fall by comparison into the background, and may unhesitatingly be neglected in the discussion of this question. A marked diminution of the albuminous contents of the blood-serum will attend chronic dysenteric evacuations, tedious suppuration, and bulky inflammatory exudations; and, in a subordinate degree, unduly prolonged lactation, and perhaps an undue abundance of other specific secretions: for the material used in forming the ingredients of the secretions is in the last instance abstracted from the albumen of the liquor sanguinis. The production of large tumours in a short space of time (hence especially the rapidly growing so-called malignant varieties) must reduce the albuminous contents of the since it is evident that their growth takes place essen- the expense of its albumen. By far the simplest mode, however, by which an impoverishment of the serum in albumen may be brought about is unquestionably *albuminuria*, whether dependent on nephritis or amyloid degeneration of the glomeruli, or other morbid condition. All these processes lead to hydræmia with certainty and rapidity in proportion as the abnormal loss of albumen fails to be neutralised by a corresponding supply of this substance to the blood. For if the hydræmia be really due to abnormal loss of albumen, if we have to do with a *hypalbuminosis* in the strict sense, it is evident that the latter may be checked by a corresponding increase in the albuminous supply; as is well known, many women not merely do not become hydræmic during a long and abundant lactation, but enjoy a condition of excellent health. On the other hand, the importance of the albumen-supply of the blood is most strikingly shown by the occurrence of hydræmia as the result of a diet very poor in albuminates, without the coexistence of any abnormal losses of albumen. Yet mere defective nutrition more often leads to general atrophy, and thereby to a diminution of the total amount of blood, with, it is true, a still greater decrease per cent. in the serum-albumen.

The circumstances in which, finally, the third form of hydræmia will be developed are contained by implication in what has just been stated. For *nephritis* might with equal justice have been cited as a cause of hydræmic plethora, owing to the lessened diuresis occasioned by it, or as a cause of hypalbuminosis, on account of the albuminuria, a symptom never absent in this disease. It is in fact precisely in the acute and chronic forms of nephritis, so-called Bright's disease, that the most extreme degrees of dilution of the blood have been determined; and good observers have seen the albuminous contents of the blood-serum fall in this affection from 8 to 5 or even 4 per cent., and the watery contents increase from 90 to 95 per cent. The specific gravity of the serum in nephritis has been repeatedly estimated at 1016 or even 1013, while the normal value is 1029—1031.*

Turning now to the question of the effect exerted by hydræmia on the circulation, we enter a province which a few years ago passed for one of the best known in pathology. *Anasarca* and *hydrops* are extremely common in hydræmic individuals; the former occurring so early, and in such marked degree, in the hydræmia due to nephritis that subcutaneous œdema is the earliest change to attract attention to the morbid condition of the blood. The following was the line of reasoning adopted. Hydræmic blood is more diffusible; consequently transudation through the vessel wall is facilitated and increased. This follows from well-known physical facts, according to which a weak solution of albumen filters more easily than a concentrated one; and it may in addition be demonstrated by a very simple experiment. When a weak solution of albumen, or still better, a simple salt solution, is injected into the peripheral end of the a. femoralis, a very considerable degree of œdema of the leg is sometimes developed—a result that can scarcely attend the injection of blood or of pure serum. The dilution of the blood-serum—it was argued further—is very rarely so extreme that any œdema or hydrops worth mentioning could be produced by it alone; but when to the hydræmic state of the blood, mechanical causes leading to an increase of transudation are added, an extreme degree of dropsy may easily be the result. To its production such factors as give rise to œdema when the blood is normal are by no means necessary; much less powerful influences suffice to produce this effect in hydræmic persons. A mechanical cause of this kind was discovered in the increase of the blood-quantum, which was supposed to elevate the blood-pressure, and it was not difficult to explain in this way the extreme œdema of nephritis. By no one has the entire doctrine been more logically carried through than by Bartels, who believed he had lent it additional support by accurately showing that the increase or disappearance of the œdema stands in an exactly inverse relationship to the diuresis.*

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* Bartels, "Krankheiten des Harnapparats," in Ziemssen's 'Handb.,' 1875, p. 87; Frerichs, 'Die Bright'sche Nierenkrankheit und deren Behandlung,' Braunschweig, 1851, p. 69.

But however simple and logical the entire deduction may appear, there are a number of facts which do not harmonise with it. First of all, it is utterly untrue that diluted blood more readily transudes through the normal capillaries than does blood of normal concentration. You may conduct a solution of no more than a half per cent. common salt, through the vessels of a rabbit's ear and continue the operation for a long time without producing the least swelling—provided only you are careful to regulate the pressure under which the injection into the artery is made so as not to exceed really low limits.* Furthermore, I do not attach any special importance to the fact that individuals may have considerable albuminuria for many years without at any time showing a trace of œdema—for this might be met by saying that in these cases hydræmia is averted by a corresponding increase in the albumen-supply. Much greater importance attaches, in my opinion, to those not uncommon instances where complete *anuria* exists for days or perhaps weeks, as may be observed after impaction of calculi, or, with unusual frequency, in hysterical subjects. There can be no doubt that a considerable degree of hydræmic plethora exists in such cases, and yet not even the slightest indication of œdema is ever observed.† Facts like these must throw suspicion on the entire doctrine at the outset; and as a matter of fact it has failed to stand the test of a thorough experimental examination.

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* See Note, p. 452.

True, the simplest form of experiment, namely, the stopping of the secretion of urine by tying the renal vessels or extirpating the kidneys of an animal, could not lead us to any result, inasmuch as this procedure would be followed by the retention in the body not only of the water, but also of the other materials excreted by the kidneys, the destructive effects of which I shall explain to you in connection with the pathology of these organs. Meanwhile, *a true hydræmic plethora* may be produced in the readiest way *by injecting a watery solution of salt into the blood*. The solution employed must be of such a strength as not to injure the blood-corpuscles; for the dog a solution of 0·6, for the horse one of 0·75, and for the rabbit one of 1 per cent. should be used. In carrying out such experiments on narcotised or curarised dogs, the injection being made indifferently into a vein or into the central end of an artery, Lichtheim* and myself were not a little surprised to find what enormous quantities of salt solution can be tolerated by the animals. We have repeatedly introduced from five to six times the blood-quantum into a dog in the space of half an hour without the appearance of threatening symptoms, and it was nothing unusual to be obliged to inject as much as 60 to 70 per cent. the body-weight in order to bring about the animal's death. When death occurred during the experiment, it was very rarely as the result of acute œdema of the lung. Rather the end was preceded by evident signs of dyspnœa; the arterial blood lost its bright red colour, the pulse became slow and intermittent, the blood-pressure curve displayed very considerable oscillations, and in the narcotised animals strong clonic spasms were of occasional occurrence. In the dogs which survived the experiment itself, the injection did not, it is true, prove permanently innocuous; yet the animals bore much larger injections of salt solution than of blood; and while the introduction of the latter to about 150 per cent. the blood-quantum always jeopardised life, we often saw dogs make a perfect recovery after we had injected an amount of salt solution equal to more than three times the blood-quantum. A still severer hydræmic plethora could hardly be recovered from.

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* Cohnheim, 'Untersuchungen über d. embol. Processe,' Berlin, 1872, p. 51.

† Bartels, l. c., p. 44; Mendel, 'Virch. A.,' lxviii, p. 294.

You will not expect the *blood-pressure* to be much influenced by the watery injections, bearing in mind your experience with transfusions of blood. How little the arterial pressure depends on the volume of the blood cannot indeed be more strikingly shown than by these experiments, the course of which in other respects completely resembles those where blood is transfused. If you inject salt solution into a dog whose arterial tension is low, *e. g.* after first dividing the cervical cord, you see a rise of pressure pretty accurately proportional to the quantity injected. If, on the other hand, a strong dog with a high normal pressure be chosen for the experiment, you may at once begin by allowing an amount of liquid equal to the blood-quantum of the animal to run into the jugular; you will see a considerable rise of the carotid pressure while the salt solution is flowing in, and then an immediate return to normal. And you may go on introducing the salt solution quite boldly, injecting about half the blood-quantum at a time, when a long period will elapse without your obtaining any other result; the only change being that as the hydræmic plethora becomes greater the interval between the rise of pressure following the injection and the subsequent fall is prolonged. The factors rendering this regulation possible have already been discussed with sufficient minuteness when treating of true artificial plethora, so that their repetition may be dispensed with here. For they are none other than the vaso-motor system in the beginning, and later on the peculiar distribution of the superfluous blood in the capillaries and veins. It is precisely in hydræmic plethora, which attains much larger proportions than the simple form, that direct proof of the abnormal fulness of the veins is afforded by the lasting elevation of pressure in these vessels. Injections of salt solution of 25 to 30 or 40 per cent. the body-weight do not cause any rise worth mentioning in the v. femoralis; but when still larger quantities have flowed in, you may wait long, and still the venous pressure does not return to its original level. We occasionally observed a permanent rise to values of 18 or even 20 mm. mercury.

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* Cohnheim u. Lichtheim, 'Virch. A.,' lxix, p. 106.

While then the blood-pressure does not behave very differently in hydræmic plethora and in the simple form, the same cannot be said of the *velocity of the blood-stream*. For the latter is very considerably accelerated, not merely during the injection, *i. e.* simultaneously with the rise of blood-pressure, *but also lastingly, long after the pressure has again become normal.* This cannot be more beautifully demonstrated than in the tongue or swimming-membrane of the frog. On placing one or other of these organs under the microscope and waiting till a regular flow is established, then slowly injecting, by means of a fine glass or metal cannula previously tied into the central end of the v. abdominalis, half or a whole cubic centimetre of a ½ per cent. salt solution, you very soon notice clear bands in the blood of the larger vessels. These are nothing but streams of salt water, which have not yet completely mixed with the frog's blood. They soon vanish, however; for the mixing of the blood and salt solution is quickly effected, certainly after a couple of circuits; and now the light-coloured blood shoots with such rapidity through the vessels that you are absolutely unable to recognise an individual corpuscle in the capillaries even, under a low magnifying power. In the veins, the peripheral plasmatic zone is usually completely free from colourless corpuscles. The striking spectacle is long enough maintained; if really vigorous animals have been chosen for the experiment, more than half an hour passes before the velocity commences to slacken, and on examining the swimming-membrane after a couple of hours you discover the blood-current to be still accelerated in no inconsiderable degree. Moreover, on each fresh little dose of salt water there ensues as before an immediate increase in the velocity of the flow.

In the dog, also, the existence of an analogous condition can be determined without difficulty. If blood be taken from the different vascular areas, the carotid, v. femoralis, v. porta, a few minutes after an injection of salt solution, the *dry residue* yielded by each specimen is approximately *equal*. The great acceleration of the blood-stream can be determined by direct microscopic examination of the mesentery, as well as by estimating prior and subsequently to injection the amount of blood flowing in the unit of time from a suitable vein, *e. g.* the dorsal vein of the foreleg; by the latter method enormous differences are sometimes revealed. Nor have we far to seek for the cause of this acceleration of the current, independent as it is of the blood-pressure. Its cause is undoubtedly the *diminution in the frictional resistance* occasioned by the passage of diluted blood through the capillaries; the liquid, having become much more watery, is not detained in the vessels of narrow calibre nearly so long as would be the case with concentrated blood. It perfectly harmonises with this view that the acceleration of the blood-stream slackens after a time; for if the more rapid flow depends on a thinning of the blood, it is natural that it should decrease as the watery contents diminish.

This brings us to the interesting question—where does the water, by which the blood has been artificially increased, remain? For that *a very considerable portion very soon for-*

sakes the vessels is proved beyond doubt by the fact that the actual estimation of the dry residue after injections of salt water invariably yields higher values than the results of calculation demand. By injecting a quantity of 0·6 per cent. salt solution, equal in amount to the blood-quantum, the dry residue of the whole blood is reduced from about 20 per cent. to 14 or at most 13 per cent.; and each subsequent injection is less and less capable of raising the percentage watery contents of the blood. There is no difficulty in making out what becomes of the missing water. During the experiment itself all the glands begin to secrete, though the order in which they do so is very inconstant. Large quantities of thin, clear urine collect in the bladder, and are passed from time to time; a profusion of saliva flows from the dog's jaws; from the intestines watery evacuations take place repeatedly; the bile also flows more abundantly; and after death the stomach and intestines are regularly found distended with turbid liquid. Almost every one of the secretions, then, is enormously increased in these experiments; but this is not all. By collecting the *lymph* flowing from a cannula tied into the ductus thoracicus immediately before its entrance into the v. subclavia, you can detect an *augmentation* of the lymph-stream which sets in directly after the first injection of salt water; and the increase and acceleration become greater with every subsequent injection, so that at last the lymph is poured out in actual jets. On one occasion, after the introduction of about 40 per cent. the body-weight, we found the velocity of the stream to be twenty-five times greater than at the commencement of the experiment. As the lymph becomes more abundant it, of course, grows clearer, *more watery*. But while this augmentation of the chyle-stream in the ductus thoracicus is very striking, an increased production of lymph is very far from general throughout the body. From the large trunks of the neck there also flows more lymph after the injection, yet the growth of the cervical lymph-stream cannot be compared with the increase of the flow through the ductus thoracicus. Far more striking, however, is the circumstance that, whether the cannula be introduced on the proximal or on the peripheral side of the glands concerned, *the lymphatics of the extremities do not* *yield a drop more fluid* than do those of an uninjured animal with undiluted blood.

With these remarkable differences, the post-mortem appearances in the animals dying during the experiments, or afterwards put to death, harmonise completely. *The abdominal organs are without exception markedly dropsical.* The peritoneal cavity never fails to contain a considerable portion of clear fluid; the mesentery and the lymphatic glands disposed in it, the pancreas, the gall-bladder, the liver, the kidneys, and the wall of the entire gastro-intestinal canal, are more or less strongly œdematous—often enormously so when the injections were very abundant, in which case the wall of the stomach may be more than 1 cm. thick. In like manner, the *submaxillary* and *sublingual* glands with the loose connective tissue surrounding them, are always highly œdematous, so much so that marked tumefaction of these regions may be observed during the experiment itself. With these organs *all the remaining ones vividly contrast by their freedom from œdema.* Neither in the central nervous system and its membranes, nor in the thoracic organs, the serous cavities, and the lungs—if we except the rare cases of pulmonary œdema—nor, as you will note, in *the entire muscular and subcutaneous cellular tissue,* is there the slightest trace of dropsy. All these parts are in no respect distinguishable from the corresponding organs of perfectly healthy animals, into whose blood not a drop of salt solution had been injected.

In order to estimate properly the significance of these facts and appearances, found by us not only in dogs, but also in rabbits, sheep, and horses, it will be advisable to compare with them the effects of *true, simple hydræmia.* No method has up to the present been devised by which the percentage albuminous contents of the blood-serum only can be reduced, while the whole of the blood-corpuscles are preserved; and if it be desired to render dogs hydræmic without adding to the blood-quantum, there is nothing for it but the removal of a certain amount of blood from a vessel and the substitution of an equal amount of 0·6 per cent. salt solution. True, to the production of simple experimental hydræmia by this method there is a limit which cannot be exceeded, for inasmuch as one dare not push the depletion beyond half the total blood-quantum without seriously endangering the animal's life, the solid residue of the blood cannot be reduced by more than half its normal amount. This, however, is a degree of anæmia which can hardly be surpassed in human pathology. If, after rendering an animal highly hydræmic, either by one, or better by several, bleedings and salt-water injections, you allow a little time to elapse and then measure its blood-pressure, this will, as a rule, be found to have fallen below normal. The fall, however, must so influence the velocity of the blood-stream that the gain which would otherwise accrue from the lessening of the frictional resistance in the capillaries does not usually manifest itself. The behaviour of the corpuscular elements of the blood shows no appreciable differences in simple hydræmia and in hydræmic plethora. Thoma* has called attention to the fact that the dilution of the medium in which the colourless corpuscles float is decidedly favorable to their amœboid movements. Whether the red blood-corpuscles are affected by the watering of the plasma, and if so to what extent, we are ignorant as yet; I have repeatedly satisfied myself that no alteration of colour or shape can be detected in them, even by employing very high powers. Moreover, the fact demonstrated by Quincke† that the unit of volume, or of weight, of blood in individuals suffering from nephritis or contracted kidney has sometimes a considerably lowered hæmoglobin-contents as compared with normal blood, does not, as will be readily understood, allow any further conclusion to be drawn from it, so long as nothing is known of the numbers of the red blood-corpuscles contained in the blood in these diseases respectively. But you will be chiefly interested in the question—how is it as regards the excretion of water from the vessels? The answer is very simple. In a dog made hydræmic in the manner described there is *neither an increase of secretion nor of transudation.* Urine, saliva, bile, gastric and intestinal secretions, are not abnormally profuse; the lymph-stream is nowhere increased, and in no organ or cavity of the body is a collection of liquid formed.

* Thoma, 'Virch. A.,' lxii,

† Quincke, 'Virch. A.,' liv.

The results obtained by these experiments on simple hydræmia appear to me to throw a clear light on the divergent results of hydræmic plethora. It is not the dilution of the blood *per se, i. e.* the percentage increase of its watery contents, that causes the augmented secretion and transudation; this is due to the larger volume, to *the increase of the bulk of the blood by the addition of so much salt solution.* Thus hydræmic plethora is a direct parallel to true polyæmia, with which, too, it perfectly accords in point of influence on the blood-pressure. The salt water is excreted just as is the superfluous blood, with only one difference—a very important one, it is true—that the excretion of the salt water is much more easily effected. But it is manifestly the same organs whose vessels are engaged in excreting the superfluous blood and the water; at any rate the increase of the lymph-stream in the ductus thoracicus, the trifling œdema of the pancreas, the slight hæmorrhagic ascites, the ecchymoses of the stomach and intestinal canal, which were all of them observable in pure artificial plethora, make unmistakably for this view. Hence we are led to the conclusion—in my opinion a very noteworthy one—that the blood-vessels of certain organs differ from all remaining ones in their behaviour towards an increase of the blood-quantum. For how else can the œdema of the salivary glands, the pancreas, the kidneys, and the other organs so often mentioned be explained? The process of secretion *per se* has clearly nothing to say to it, for however energetically the production of saliva may take place in a healthy, uninjured dog, for example, not a drop more lymph will ever flow into or out of the cervical lymphatic trunk in consequence. Moreover, with regard to the pancreas, a gland which does not secrete constantly, but only under certain conditions, Lichtheim and I have several times succeeded in determining the occurrence of a very high degree of œdema of the organ, although during the injection of salt water not a drop of fluid flowed from a cannula tied into the canal of Wirsung; in the submaxillary gland we have occasionally seen a similar state of things. Yet it cannot be purely accidental that the organs which become œdematous in hydræmic plethora should be precisely those whose phy- l function consists in the *separation of a watery secre-*

tion. On the contrary, I believe our experiments lead to not unimportant conclusions with respect to the mechanism of secretion. For they show that the blood-vessels of the secreting glands differ from those of the remainder of the body in being normally so constituted as to allow of the ready passage through them of water and watery solutions. We are, it is true, entirely ignorant of the manner in which this peculiar property of the gland-vessels is utilised in secretion. The plethora experiments, however, teach at least that a very great increase of the blood-quantum, and more especially an absolute augmentation of the water of the blood, can, without the co-operation of the secretory nerves or cells, cause an increased transudation of fluids from these vessels. These transudations may in part be employed in the production of secretion, if the other conditions are fulfilled; but it is not necessary that they should be, nor are they always, so employed; and even the most active secretion apparently cannot keep pace with the transudation ensuing on an intense hydræmic plethora. Hence the never-failing and often powerful *augmentation of the lymph-stream* from the implicated organs, and hence the occurrence of *œdema* when the augmentation at last becomes insufficient. That the liquid should be diffused in the vicinity of the glandular organs involved in the œdema is not at all strange; in this way the œdema extends from the gastric mucous membrane to the submucous tissue, and from the lymphatic glands of the mesentery to the mesentery itself. In like manner the ascites originates, while the serous cavities of the thorax and of the central nervous system remain perfectly dry.

The entire doctrine of hydræmic, or, as it is also called, *cachectic* dropsy, is, you perceive, untenable in the form in which it was current till recently. Simple hydræmia is not a cause of œdema; and if the œdema of nephritis really depended on hydræmic plethora, the localities in which it first appears would be very different to what they actually are; *anasarca* in particular could never occur, though it is precisely the dropsy of the skin that is characteristic of renal inflammation. For the rest, it is more than doubtful whether hydræmic plethora ever attains such magnitude in human beings as to produce the *specific* œdemas with which we have become acquainted through experiments on animals. But however incontestable this conclusion appears, it does not in any way alter the fact that dropsy is very commonly associated with a hydræmic condition of the blood; and if the old explanation cannot satisfy us we must make it our business to look for another which will harmonise better with the results of experiment. As to the direction in which an explanation should be sought there is no lack of valuable indications. *Only while the vessels are fully intact*, and so long as the blood-stream continues *regular* in other respects, do they behave towards hydræmia and hydræmic plethora in the manner described. You are aware that œdema of the leg never ensues on simply ligaturing the v. femoralis of a healthy dog; while if a considerable quantity of salt water be injected into a dog with a ligatured femoral vein, the extremity swells, not always, but in a large proportion of cases. Set up inflammation in the hind paw of a dog, and introduce a cannula into the lymphatics of the leg on each side. When you have determined the amount of lymph flowing from each of the cannulæ, allow a couple of litres of salt water to run into the v. jugularis; you will at once perceive that, while the lymph flowing from the sound side undergoes no alteration, *the increase on the inflamed side is very considerable*, and the fluid at the same time more watery. In inflammations so trifling that a tumor is almost or altogether absent, *e. g.* in erythema of the skin, hydræmic plethora at once causes a really considerable swelling. Nothing of the kind is observable in simple hydræmia—at any rate not immediately on the replacement of a certain quantity of blood by water. But when the hydræmia so produced *persists for a few days*, when a certain amount of blood is daily replaced by salt water and the percentage watery contents is in this way permanently maintained at a tolerably high value, then ligature of the v. femoralis leads to œdema of the leg in these animals also, and there is present around the seat of operation a very considerable inflammatory wound-œdema, which almost never appears in dogs with undiluted blood.

These facts, I think, provide the key to the comprehension of hydræmic œdema. If we see dropsy setting in anywhere in hydræmic individuals we should ask first of all whether conditions are present in the part affected *by which the permeability of the vessel walls is abnormally increased.* This is true of the skin in precisely those forms of nephritis in which marked anasarca sets in earliest, *e. g.* in the *scarlatinal form;* so much so that, as is well known, œdema of the skin occasionally occurs in scarlet fever without any impoverishment of the blood by antecedent albuminuria. Moreover, for those cases of chronic nephritis where the repeated exposure of the body to cold and wet is set down as the ætiological factor, we shall scarcely seem too daring, if we assume, as the basis of the anasarca, an inflammatory alteration of the cutaneous vessels, developed simultaneously with the kidney affection, and called forth by analogous causes. True, a similar condition does not obtain in the cachectic dropsy seen in persons who are hydræmic from other causes. But the œdemas and dropsies of this kind are not nearly so considerable nor so rapid in their development; rather they are restricted as a rule to swelling of the ankles with a moderate amount of dropsical effusion into the serous cavities; and a long illness is usually necessary to their development. It appears to me, however, that the conclusion to be drawn from the facts above noted regarding simple hydræmia of somewhat long duration is especially worthy of attention. If a ligature applied to the vein causes no swelling of the leg where the hydræmia is quite recent, but gives rise to œdema of the extremity when the animal has been for a considerable time hydræmic, I can come to but one conclusion, namely, that *a hydræmia of somewhat long duration itself injures the vessel walls and increases their permeability.* Nor can the existence of such a condition be indifferent to the heart; at any rate the low pulse-wave of the hydræmic is a sufficiently clear indication of a falling off in the energy of the cardiac contractions. Now, if you call to mind that weakness of the heart forms an obstacle to the emptying of the venous system, and therefore easily raises the tension in it above the normal, you will have no difficulty in understanding why individuals who have been a long time hydræmic should develop dropsical swellings and effusions in different parts of the body.

Let us sum up the results arrived at from the discussion whole subject of hydræmia and its relation to dropsy.

A lasting hydræmic plethora does not exist, because the superfluous water, like the superfluous blood in simple plethora, is separated by the vessels *of certain organs.* The water so separated becomes mingled with the secretions of these organs *and is thus discharged from the body;* and if the separation is too considerable for the secretions to keep pace with it, the water enters the *lymphatics, or penetrates into the interstices and cavities of these organs, and of those in their immediate neighbourhood, where it gives rise to œdema and dropsy.* On the other hand, while the blood-stream is normal, *simple hydræmic or hypalbuminotic blood transudes no more readily through healthy vessels than does undiluted blood;* it does so, however, when the permeability of the vessels is *increased* from any cause. Such a cause is presented by the hydræmic quality of the blood itself; and œdemas and dropsies are in consequence very easily produced as a result of *long-enduring* hydræmia, more particularly in localities where the venous stream has to overcome the action of gravity.

Directly contrasting with hydræmia are the processes by which the watery contents of the blood are diminished, and its concentration therefore increased. This condition can be developed to a certain extent in animals by simply depriving them of water, as *e. g.* by feeding rabbits with dry barley instead of with succulent cabbage or carrots. But far larger quantities of water may be withdrawn from the blood of an animal by a method proposed by Wegner,* and further elaborated by Maas;† namely, the injection of a very concentrated solution of salt or sugar into the peritoneal cavity. The effect of this is to cause a transudation of water from the vessels of the peritoneum into its cavity in such abundance that the blood becomes quite concentrated. In man a considerable degree of concentration of the blood follows very profuse *sweating,* and still more certainly ensues as the result of copious *watery effusions into the gastro-intestinal canal* and the removal of these from the body, such as occur after the use of powerful purges, and above all in a disease, of which abundant, watery, saline, non-albuminous evacuations *per os et anum* are pathognomonic, namely *cholera*. In the choleraic seizure the blood is so concentrated as to acquire a tar-like consistence and quality. What are the consequences to the circulation? First and chiefly a really enormous *increase of the frictional resistance in the capillaries*, and, as a result of this, such a considerable retardation of the flow that the entire circulation must suffer in the extreme. Next, granted that the loss of volume is compensated by the adaptation of the arteries to their lessened contents—though this can hardly take place in the severer degrees of concentration—the delay of the stream in the capillaries must so reduce the amount of blood entering the heart during diastole as to lead to an important *lowering of the arterial pressure*. Further, the fluids bathing the parenchyma and cavities must disappear, inasmuch as they are greedily sucked up by the concentrated blood. Instead of the œdema of hydræmia we have here a general abnormal *dryness;* the lungs, muscles, &c. lose their natural turgor and acquire a leathery consistence; the serous surfaces are covered with a scanty, viscid, tenacious juice, which can be drawn out into threads; the skin of the whole body shrinks, and at the same time, like the visible mucous membranes, acquires a markedly *livid* hue, owing to the extreme retardation of the blood-stream, which allows of a very complete diffusion of the oxygen of the blood-corpuscles. This, however, is not the only effect exerted on the blood-corpuscles by the concentrated blood-plasma. In most the amœboid movements are greatly interfered with, and while this indicates an inability on the part of the white corpuscles to accommodate themselves properly to their altered medium, *the presence of potash salts in the plasma* very clearly shows that the red corpuscles are still more seriously injured. Moreover, Maas has observed in his experiments an actual solution of red corpuscles with consecutive *hæmoglobinuria*. No such certain evidence can be adduced in proof that the heart and vessels are injuriously affected by a loss of water from the blood. True, there can be no question that the extreme retardation of the blood-stream in the coronary vessels must impair the functional power of the heart and the energy of its contractions; but th[illegible]tration of the blood appears to be always *of too transitory a character* to give rise to lasting changes in the myocardium or vessel walls. Where the loss of water is extreme the choleraic seizure proves fatal; but when the attack is survived, nothing can be more simple than the restoration of the watery contents of the blood to its original standard by the drinking of large quantities of liquids. Whether the blood ever becomes so concentrated from profuse sweating as to lead to serious circulatory disturbance is very questionable. In those cases of *insolation,* at least, where the fatal termination is preceded as a rule by extraordinarily profuse perspirations, we have, coincidently with the anhydræmia, the influence of the abnormally high external temperature, to which the lion's share in producing the phenomena of sunstroke undoubtedly belongs. The concentration of the blood due to water-inanition is evidently too slight to affect the heart and vessels to any considerable extent. As regards the withdrawal of water by artificially increasing the diffusion into the abdominal cavity, we know only that it may prove fatal to rabbits, but are ignorant of the effects of this condition when prolonged.

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* Wegner, 'Langenb. A.,' xx, p. 51.

† Maas, 'Bericht über d. 10 Chirurgencongress,' p. 5; 'Beilage z. Ctbl. f. Chirurgie,' 1881, No. 20.

CHAPTER IX.

CHRONIC ANÆMIAS.

Relations of spleen, lymphatic glands, liver, and bone-marrow to the life-history of the blood-corpuscles.—Secondary oligocythæmia and leucocytosis.—Solution of red blood-corpuscles.—Chlorosis.—Essential anæmias.—Appearances presented by the blood in the latter.—Microcytes.—Anæmia splenica.—Pseudoleukæmia.—Pernicious anæmia.—Leukæmia.

Action of anæmia on the circulation.

Fate of bacteria and hyphomycetæ present in the blood.

WHILE discussing the pathology of the *liquor sanguinis* we had a tolerably certain basis of fact to go upon ; but this unfortunately is very far from being the case when we turn our attention to the morbid disturbances to which the *blood-corpuscles* are liable. As regards the blood-plasma, we were able to state pretty accurately the conditions under which its watery contents are increased or diminished ; but how imperfect, on the other hand, our knowledge of the fate of the blood-corpuscles is, was lately pointed out to you. A rational solution of the entire problem cannot of course be arrived at till we become acquainted with at least the main outlines of the physiology and pathology of *the blood, that is, of the organs engaged in the production and destruction of the blood-corpuscles ;* but so far, we have hardly taken the first steps toward the acquisition of this knowledge. I lately called attention (p. 430) to the different interpretations of which the facts bearing on the *physiological* function of the *spleen* are capable, and insisted that a destruction of red corpuscles is the only one of its supposed functions which can be defended on solid grounds. But the results too of experiment and of pathology have also been meagre enough, and are more calculated to suggest problems for solution than to solve them. Extirpation of the spleen[*] has often been survived by dogs, and a few times by human beings, without any injurious results; and the enlargement of the lymphatic glands frequently observed after this operation appears to indicate that the latter take upon them vicariously the work of the spleen. Stimulation of the nerves supplying the spleen causes a *diminution in the size* of the organ; their division is followed by an *increase in its size,* which after a time gradually disappears.[†] But the statements as to whether the number of colourless corpuscles in the general circulation is increased, unchanged, or even diminished after the neurotomy are so contradictory that no conclusion can be drawn from them. According to some, the supply of white corpuscles from the enlarged spleen to the vascular system is more abundant;[‡] according to others there is a storing up in the spleen of colourless cells, which must of course be withdrawn from other parts. In like manner, some writers[§] believe that the number of white corpuscles is increased by contraction of the spleen, others[||] that it is diminished. *Pathological enlargements* of the spleen, both acute and chronic, are, as is known, some of the most commonly met with changes. The acute form occurs, *e. g.* in infective diseases, and in many inflammations (chiefly, it is true, of an infective character); and a portion of these hyperplasias may unhesitatingly be regarded as *inflammatory.* We meet with chronic enlargements of the spleen in individuals who have had repeated attacks of intermittent fever; as the result of lasting venous congestion, in cases of insufficiently compensated cardiac lesions and of cirrhosis of the liver; in certain diseases, as the so-called anæmia splenica or pseudoleukæmia, and above all in leukæmia, where the organ may attain an enormous size. But as regards the condition of the blood in all these cases, the greatest conceivable differences are met with. In acute tumefaction of the spleen there is often a moderate amount of *leucocytosis*, more especially in the swelling which occurs in inflammations. Neither the chronic tumor of intermittent fever, nor that of anæmia splenica is accompanied, any more than is the induration from engorgement, by an increase of white corpuscles; indeed, statements are to be found in the literature of the subject,* according to which the contents of the blood in colourless cells is diminished both in the acute swelling of the intermittent attack and in the chronic tumor of fever. In leukæmia the very contrary is the case; for here the white corpuscles in the blood are regularly multiplied, occasionally to an incredible extent—proof enough evidently that hyperplasias of the spleen are of very different dignity and importance. In what way amyloid degeneration, either of the follicles or the capillaries, influences the composition of the blood we are altogether ignorant. Atrophic processes affecting the entire spleen do not exist except in association with general emaciation and a corresponding decrease of the blood-quantum; so that no conclusions as to the function of the organ can be drawn from them. Partial destruction affecting smaller or larger sections of the organ, *e.g.* by infarction, can be compensated simply by the vicariously increased action of the remainder.

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[*] G. Simon, 'D. Exstirpation d. Milz am Menschen, &c.,' Giessen, 1857; F. Führer und H. Ludwig, 'Arch. f. phys. Hlk.,' xiv, pp. 315, 491; Péan, 'L'Union méd.,' 1876, No. 89; cf. Nedopil, 'Wien. med. Woch.,' 1879, Nos. 9—11; Czerny, ibid., Nos. 13—17.

[†] Schiff, 'Leç. sur l. phys. de l. digest.,' 1867, ii, p. 416; Jaschkowitz, 'Virch. A.,' xi, p. 235; Mosler, 'D. Path. u. Therap. d. Leukæmie,' Berlin, 1872; Bulgak, 'Virch. A,' lxix, p. 181; Jerusalimsky, 'Ueber d. physiol. Wirkungen d. Chinin,' Berlin, 1875.

[‡] Tarchanoff, 'Pflüg. A,' viii, p. 97.

[§] Drosdoff und Botschetschkaroff, 'Med. Ctbl.,' 1876, p. 81.

[||] Bulgak, l. c.; Tarchanoff und A. Swaen, 'Arch. d. phys.,' 1875, p. 324.

Our knowledge of the physiology and pathology of the *lymphatic glands* is little more advanced. Here too mere comparative observations of the inflowing and outflowing lymph are open to different interpretations; and the solution of the question has scarcely been attempted from the experimental side. Extirpation of lymphatic glands cannot of course decide anything, inasmuch as numbers remain to step into the breach. That neither the concentration, nor the quantity of colourless and red corpuscles contained in the lymph flowing from the inflamed paw of a dog is altered after passing through the glands has been shown by Lassar;* he was also able to determine that the lymph contained in the v. efferentia of inflamed lymphatic glands is highly concentrated and rich in corpuscles. This, however, is really all we know of the influence exerted on the outflowing lymph by circulatory disturbances in the lymphatic glands; the effects of arterial or of passive congestion, as well as of stagnation in the glands, have not been investigated as yet. Pathology, though the opportunities for occupying itself with the lymphatic glands are sufficiently numerous, has so far done little to elucidate their function. Enlargements of these glands are perhaps still more common than are those of the spleen, and may either be markedly inflammatory, going on even to suppuration, or such as fall within the category of tumours, *e. g.* lymphomata and lymphosarcomata. All these either do not alter the composition of the blood, or at most give rise to a certain amount of leucocytosis; while the leukæmic hyperplasia of the lymphatic glands, like that of the spleen, may cause an unlimited increase of the colourless blood-corpuscles.

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* Kelsch, 'Arch. d. phys.,' 1876, p. 490.

The pathology of the liver will meet with careful consideration later on; but unfortunately I shall have very little to say on that side of its activity which concerns the fate of the blood-corpuscles. That red corpuscles are disintegrated and used up in the liver is not indeed open to doubt; yet we know nothing whatever of the details of this disintegration, of the extent to which it takes place physiologically, or whether it is at all influenced by pathological processes. Whether, as has been positively shown to be the case during uterine life, more particularly by Neumann,† a new production of red corpuscles also takes place in the liver during extra-uterine life, —according to the view of a few writers who rely on the presence of certain slightly flattened tolerably resistant forms of red corpuscles in the blood of the hepatic vein—cannot to my mind be denied or strictly proved at present.

Lastly, for a pathology of the *bone-marrow* a foundation of fact is wanting. As I was obliged to confess on a recent occasion, we are not by any means so well acquainted with the fate of the cellular elements of the medulla as to dispense with hypothesis. The reasons which justify us in regarding the nucleated red blood-cells as a preparatory stage of the non-nucleated ones, I lately communicated to you (p. 432); and I did not conceal the divergency of opinion which at present prevails as to the modus of their formation. According to one view they arise by the transformation of certain colourless cells, according to another their origin and multiplication are supposed to be due to cell-division. Intimately connected with our ignorance of this subject is the impossibility of stating with any certainty in what relation the colourless contractile marrow-cells stand to the blood, although there is much to indicate that colourless cells are being constantly produced in the medulla, that these penetrate the capillaries, and thus become mingled with the blood-stream. Nor does experience of the diseased bone-marrow throw much light on the subject. You will not expect an inflammation, an osteomyelitis, to lead to any alteration in the composition of the blood, since it never affects more than one, or at most a few, of the bones. And further, there are tumours of the medulla, *e. g.* myelogenic sarcomata, which have not the least influence on the blood; while, on the other hand, with a leukæmic hyperplasia of the bone-marrow there is found the same increase of the white corpuscles as occurs in the analogous diseases of the spleen and lymphatic glands. Still less light, if possible, is thrown on the history of the coloured elements of the blood by the pathology of the bone-marrow. Blood-corpuscle-containing cells, such as have long been known in the spleen, are, it is true, met with in varying numbers in the bone-marrow of persons affected by very different acute and chronic diseases, more especially when associated with wasting; they are very common, for example, in leukæmic and anæmic cases. If these bodies be left out of account, our knowledge is reduced substantially to the single fact determined by systematic examinations of the bone-medulla during the last few years, namely, the occurrence of extraordinary numbers of *nucleated red blood-corpuscles* in the marrow of individuals who have perished from a *condition of extreme anæmia*—individuals whose medulla might at their time of life be expected to contain only the ordinary non-nucleated discs, or at any rate a great preponderance of these.

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* Lassar, 'Virch. A.,' lxix, p. 516.

† Neumann, 'Arch. d. Hlk.,' xv, p. 441.

I need hardly say that a rational pathology of the corpuscular elements of the blood cannot be built up on such feeble and uncertain foundations. If we ask ourselves, in what way can changes in the number or constitution of the blood-corpuscles come about, it might at first sight appear a very simple and natural classification of the disturbances under discussion, to distinguish between the noxæ which act directly on the mature blood, and those which first affect the blood-producing organs, and by consequence indirectly influence the blood itself. Nevertheless, however correct from a theoretic standpoint such a division may appear, on attempting thus to analyse the morbid conditions of the blood, we are at once met by the most serious difficulties. In many cases our knowledge is not at present sufficient to enable us to determine with accuracy the causes of these conditions, and this difficulty is still further enhanced by the facts that the composition of the blood is incessantly varying, and that there is as a result a never-ceasing reciprocal action between the blood and the blood-producing organs, on the one side, and the continuous progress of the processes of new formation and disintegration of the blood-corpuscles, on the other. For this reason a strict separation of the events connected with the mature blood from those connected with the blood-producing organs appears impossible. Under these circumstances, it will certainly be most prudent, in discussing this subject, to set out from facts, *i.e.* from the observed pathological changes in the number and constitution of the blood-corpuscles.

All these conditions have one common character, namely, *the poverty of the blood in normal functional red corpuscles.* Hence they are usually called in a general way, *anæmias*, although this term should properly be restricted to the diminution of the blood as a whole, while the processes under discussion would be more correctly designated *oligocythæmias*. Yet the latter are so intimately related, not only to the true anæmias, but to the hydræmias also, that it is hard to say where the one begins or the other ceases. By hæmorrhage the amount of the blood as a whole is first reduced. Soon, however, the lost water is restored by the entrance of the lymph and chyle into the vascular system; the colourless corpuscles, of which comparatively fewer have been lost than of the specifically heavier red corpuscles, are also more quickly replaced; and the result is a condition of some permanency, characterised chiefly by a diminution in red blood-corpuscles, which are, as we have seen, regenerated last and most slowly of all. In defective nutrition it is similarly the red corpuscles that suffer most essentially, apparently because such of them as are used up in tissue-metabolism are then replaced with extreme difficulty. Pyrexial affections also exert an especially destructive action on the red corpuscles; and if the organism has to discharge any abnormal task whatever, *e. g.* in suppuration or in the production of large and rapidly growing tumours, the red corpuscles do not suffer least. For the material consumed in building up the tumour is lost to the blood-producing organs, and hence the red blood-corpuscles, being the last stage and at the same time consummation of blood production, must chiefly fall short. In all these conditions a peculiar constitution of blood, agreeing in its essential features, becomes established; the blood is *poor in red corpuscles* and therefore presents a moderate degree of *leucocytosis*, while the albumen of the serum is reduced, and a *certain amount of hydræmia* present in consequence.

But in addition to these anæmias or oligocythæmias there are some special processes, affecting chiefly the red blood-corpuscles, which demand a brief notice. It is by no means rare for a number of red corpuscles to be *dissolved* in the circulating blood, so that their hæmoglobin is set free in the serum. I already stated (p. 439), when speaking of transfusion, that this occurs when blood from another species is introduced into the vascular system; but as a large number of reagents have a solvent action on the blood-corpuscles, *e. g.* glycerine, ether, distilled water, the solution may be experimentally effected in a variety of ways. The same result, however, ensues in certain pathological conditions; it appears to follow snake-bites, and occurs in yellow fever, in extensive *burns*, but more certainly still where *salts of the bile-acids* gain access to the blood, for there is hardly a better solvent for blood-corpuscles than these latter. I have on previous occasions partially described the immediate effects of the solution in the circulating blood of a tolerably large quantity of red blood-corpuscles. You will remember the experiments of Naunyn (p. 238) on the acute formation of thrombi, following the injection into the vascular system of transparent blood, of such reagents as rapidly dissolve large numbers of red blood-corpuscles, or even of pure hæmoglobin solutions. True, that thrombosis does not always follow the entrance of free hæmoglobin into the serum is not surprising; for if, as we have the most cogent reasons for believing, the process is one of *ferment intoxication*, it is to be inferred not only that the *quantity* of dissolved blood-corpuscles is one element of essential importance, but also that, with respect to the action in the circulation, it is not immaterial by what means and in what way the solution of the blood-corpuscles is effected. Everything depends on whether or not much fibrin-ferment has been set free. Because blood that has been rendered transparent by freezing possesses a high fermentative energy, its injection gives rise as a rule to thrombosis, while such an occurrence is practically unknown when distilled water is injected into the blood of a living animal. The resorption of salts of the bile-acids into the blood, which always attends any considerable degree of *icterus* is also non-productive of this result, at least in the vast majority of cases. It is most probable that the small quantities of ferment, originated during the slow and gradual absorption of cholates into the blood, are at once decomposed by the vital power of the vessel walls, while in the mixture of distilled water with the blood very little ferment at all is produced.

We also mentioned that, when free hæmoglobin enters the blood-serum in large quantity in a short period, it passes over into some of the transudations,* chiefly into the urine—*hæmoglobinuria* sets in. This condition ensues with such regularity and constancy whenever red corpuscles in considerable quantity are rapidly dissolved, while, on the other hand, we are up to the present unacquainted with any other process by which the entrance of hæmoglobin into the urine could be brought about, that we hold ourselves justified in concluding even that every hæmoglobinuria points to a rapid destruction of large numbers of red corpuscles—a matter about which you will hear more in connection with the pathology of the urine. It must be carefully noted, however, that for the production of hæmoglobinuria the solution of *a considerable quantity of corpuscles in a short space of time* is necessary; the presence of a certain amount of free hæmoglobin in the blood-serum is essential, and this is not secured when the corpuscles are gradually dissolved in minute portions. There has been the most active discussion as to what takes place under these circumstances, and even now opinions differ somewhat. Certain it is that the appearance in the urine of the *colouring matter of the bile* has been frequently determined; yet we have recently become aware that the excretion of bilirubin is usually preceded or accompanied by an excretion of *urobilin*. At the same time a yellow discolouration of the juices of the parenchyma and hence of some of the organs and tissues themselves may take place; this is termed *icteric*, although here too it is by no means certain that the colouring matter in question is really bilirubin. It is, moreover, still an open question whether the metamorphosis of the freed hæmoglobin occurs in the blood or, as is more probable, in the tissues (of the liver, for example); in which latter case the passage of the colouring-matter or matters into the urine would be effected by reabsorption into the blood. All things considered, it certainly cannot be affirmed that the doctrine of *hæmatogenous icterus*, as it is called to distinguish it from the mechanical, hepatogenous jaundice, at present occupies the position of a complete and well-rounded domain of pathology.

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* Virchow, 'Dess. A.,' i, p. 379; Kühne, 'Virch. A.,' xiv, p. 32; Naunyn, 'A. f. Anat. u. Phys.,' 1868, p. 401; Steiner, ibid., 1873, p. 193; Tarchanoff, 'Pflüg. A.,' ix, p. 53; Naunyn, ibid., p. 566; Hoppe-Seyler, ibid., x, p. 208; C. Gerhardt, 'Correspdzbl. d. thüring. allg. ärztl. Vereins,' 20 Nov., 1878; Kunkel, 'Virch. A.,' lxxix, p. 455.

While we were able in the foregoing cases to determine without much difficulty the cause of the falling off in red blood-corpuscles, we now come to a series of processes in which, though the diminution of the coloured constituents is none the less certainly established, the pathogenesis of the condition is by no means satisfactorily cleared up. Amongst them is an affection which approaches in many respects the severe forms of icterus just discussed, namely, acute phosphorus-poisoning. Some time ago it was shown by Bauer* that in this affection the absorption of oxygen may be reduced to nearly half its normal value; and more recently A. Fränkel and Röhmann* determined by counting that a progressive decrease of the red corpuscles of the poisoned individuals takes place—slowly at first, but afterwards quite rapidly. There is, however, at present no certain indication as to what this very remarkable fact is attributable to. Still greater interest attaches to certain independent *chronic* diseases, of which the first I shall mention, though so common and clinically well marked, is none the less enigmatical in its essence, namely, *chlorosis*. It is, as is well known, chiefly women who are attacked by this disease—more especially in early life about the age of puberty; so that the hypothesis which connects it with the processes of sexual development was obvious enough. The alteration of the blood in chlorosis undoubtedly consists in a considerable reduction of the coloured constituents, so much so that Quincke† found the hæmoglobin contents of chlorotic to be still less than that of leukæmic blood. In many cases of chlorosis, while the number of the red corpuscles was found to be quite unaltered and the diameter of the single corpuscles normal or even increased,‡ the colouring matter contained in them was seriously diminished.§ Nevertheless, it would be a mistake to regard this circumstance as pathognomonic of chlorosis. For there is no doubt that at least in severer cases the *number of the red blood-corpuscles is also reduced*, sometimes extremely so, it may be to less than half the normal amount. A slight degree of leucocytosis is then present, while at other times the relative numerical proportions of the two kind of blood-corpuscles in chlorotic blood do not deviate from the normal; and the same may be said of the albuminous and watery contents of the serum. It must be honestly confessed that the cause of this blood-change, and its manner of origin, are still merely conjectural. Anatomical examination of chlorotic women has often revealed a certain amount of narrowness of the large arteries and thinness of their walls—especially of the aorta—and at other times defective development of the genitals; but in the hæmapoietic organs nothing has been discovered which would throw light on the peculiar alteration of the blood. On the other hand, the long-known remedial value of iron, of which Hayem* claims to have shown that under its influence the blood-corpuscles become redder, unquestionably favours the notion that the materials necessary to blood-production, more particularly the iron, are deficient in the nutriment absorbed by the chlorotic; either because too little iron is taken in a readily digestible form, or because, as Zander† has recently maintained, the gastric juice of the chlorotic is too poor in hydrochloric acid. Do not, however, be led into supposing that the present state of our knowledge admits of our giving a decisive opinion on the claims of this hypothesis.

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* Bauer, 'Zeitsch. f. Biol.,' vii, p. 53.

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* A. Fraenkel u. Röhmann, 'Zeitschr. f. phys. Chem.,' iv, p. 439.

† Quincke, 'Virch. A.,' liv, p. 537.

‡ Malassez, 'Compt. rend.,' lxxxv, p. 348.

§ Duncan, 'Wien. akad. Stzgsb.,' 1867, lv, p. 516.

For a long time past the attention of physicians has been engaged by certain cases of disease, which, while bearing a general resemblance to the chronic anæmias, yet betray so much that is peculiar in their etiology, anatomical and microscopical appearances, as well as in their course, that it has been thought right to expressly distinguish them from the ordinary remaining forms by the name, *essential anæmias*. The feature which is constantly repeated in all these cases, and which imprints on the whole picture its characteristic expression, is the decrease in the coloured constituents of the blood, the *hæmoglobin contents*. It is more difficult to determine, on the other hand, whether a diminution of the blood as a whole, a *true* anæmia is present—in favour of which the post-mortem examination seems in many cases clearly to speak—or whether *a morbid condition of the red blood-corpuscles* is the only factor at the bottom of the entire disease. It has repeatedly been made out that the red corpuscles are *paler*, and therefore contain less hæmoglobin than normal. Still more frequently, however, there has been found a reduction—often very considerable—in the number of the corpuscles contained in the blood of these patients: it may perhaps be said that this *oligocythæmia* is never absent in pronounced cases. Were this all, you would be justified in asking for what reason should these essential anæmias be distinguished from chlorosis. There is, however, a large number of facts, proving only too clearly that these cases have no connection whatever with ordinary chlorosis. It is at the outset sufficiently remarkable that the essential anæmias are by no means so regularly confined to the period of puberty in the female, but may be observed at all ages and in both sexes. Furthermore, experience has but too frequently shown that the essential anæmias, in contrast to chlorosis, manifest themselves as severe diseases which defy all therapeutic measures, in particular the treatment by iron, and in the majority of cases directly lead, after a short or more protracted course, to a fatal termination. Add to this that microscopic examination of the blood, which has naturally been considered the best means of obtaining information, reveals some peculiarities which are not found in chlorotic blood. Remarkably small red blood-corpuscles, so-called *microcytes*, have repeatedly been seen in these cases. It has indeed long been known that the size of the red corpuscles, circulating in the blood of the same individual, is not absolutely uniform, and that, scattered amongst the vastly preponderating majority of ordinary red corpuscles, there are always a few disks whose diameter is considerably below the average. Manassein* has discovered, by a series of direct experiments, that the blood-corpuscles of healthy animals undergo certain variations of size under the influence of manifold agencies—such as alterations of the gaseous contents, of temperature, the addition of some reagents, &c.; of these the *diminution in the size* of the corpuscles in pyrexia and in dyspnœic blood is probably the most interesting. Yet the small corpuscles of healthy or of pyrexial blood cannot compare with the microcytes of essential anæmia. The latter fall very considerably short of the size which Manassein succeeded in producing experimentally. Diameters of from 2 to 4 $\mu\mu$. have been measured by various observers, not merely in a few corpuscles, but often in large numbers of them together; the great majority even of the coloured corpuscles may have the dimensions just named. With their reduction in size, the blood-corpuscles lose their discoidal form and central depression. They become globular and quite similar to those which M. Schulze has taught us to separate from the normal blood-corpuscles by raising the temperature; they never show a tendency to arrange themselves in rouleaux. In colour they are occasionally uniform with normal corpuscles, or even of a still deeper red; but they are often decidedly paler. The statements put forward in the literature differ extremely as to the relative quantities of microcytes present in the various cases. Eichhorst[*] looks upon them as a constant factor in so-called pernicious anæmia, and considers that they are present in quantities directly proportional to the severity of the case. By others,[†] not only is the latter statement disputed, but doubt is thrown on their constancy in the disease just named. Vanlair and Masius[‡] found enormous numbers of them in the blood of a woman who presented the symptoms of general anæmia, but who nevertheless completely recovered after an illness of some months' duration; in this case the microcytes gradually gave place to ordinary blood-corpuscles. The *transitory* appearance of microcytes has been witnessed in chronic anæmias and during convalescence from severe diseases by several other observers—most strikingly by Litten[§] in a phthisical patient aged twenty, with greatly enlarged mesenteric, cervical, and axillary glands. An examination of the blood carried out four days before death revealed almost nothing but small red microcytes, of which not a trace could be found either before or afterwards, although the succeeding examination was undertaken after only three hours had elapsed. If the observation of this case was correct, it is certainly eminently calculated to throw discredit upon single examinations of the blood, and at any rate to inculcate caution in drawing conclusions therefrom.

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* Hayem, 'Compt. rend.,' lxxxiii, p. 985.

† Zander, 'Virch. A.,' lxxxiv, p. 177.

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* Manassein, 'Ueber d. Dimensionen d. rothen Blutkörperchen unter verschiedenen Einflüssen,' 1872; 'Med. Ctbl.,' 1871, p. 689.

There have also been seen in the blood of anæmic persons biscuit- or club- and bottle-shaped blood-corpuscles, as well as corpuscles with so deep a central depression that a completely annular form was the result—and this by such good observers[*] as apparently to exclude the possibility that the alteration in shape was due to the method of preparation. No such doubt can suggest itself with regard to the occurrence of *conspicuously large* red blood-corpuscles which have repeatedly been found in anæmic blood, and the same may be said of the sharply characterised and absolutely unmistakable *nucleated red blood-corpuscles*. You see how great are the differences in the form and size of the corpuscles, and how very right Quincke is in speaking of a poikilocytosis in anæmias. If we except a few older isolated observations on the blood of leukæmia, the nucleated red corpuscles were first seen by several observers[†] in the blood of individuals after death from pernicious anæmia. More recently, however, Ehrlich[‡] has succeeded, through the employment of improved methods, especially the judicious staining of preparations of dried blood, in determining their presence in the living during a longer or shorter period in all cases of severe anæmia.

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[*] Eichhorst, 'Med. Ctbl.,' 1876, p. 465; 'Die progressive perniciöse Anämie,' Leipsig, 1878.

[†] Rosenstein, 'Berl. klin. Woch.,' 1877, No. 9; Litten, ibid., No. 19; Lépine, 'Rev. mensuelle,' 1877, No. 2; Quincke, 'D. A. f. klin. Med.,' xx, p. 1.

[‡] Vanlair et Masius, 'Bull. de l'acad. de méd. de Belgique,' v, 3 série, No. 6, 1871.

[§] Litten, 'Berl. klin. Woch.,' 1877, No. 1; cf. also the similar observation of Lépine and Germont, 'Gaz. méd. de Paris,' 1877, No. 18.

Are these results sufficient to allow of our constructing from them a special group of diseases—the essential anæmias? For a long time it appeared so, and Eichhorst[§] believed he had discovered in the presence of the microcytes a pathognomonic sign of idiopathic essential anæmia. Yet the erroneousness of this view might have been apparent from the first. For not only are the microcytes, as already stated, absent in many cases of extreme pernicious anæmia, but it has furthermore come to light that identical forms occur in anæmias, which the previous history of the patients most clearly show to have been secondary; Quincke's numerous clinical records afford the most conclusive evidence of this. With the nucleated corpuscles it has fared no better. For all the hopes of an explanation of this enigmatical disease, which were first excited by their discovery in the blood, and still more in the bone-marrow, of persons dead of pernicious anæmia, have turned out fallacious. Ehrlich* has found the same elements in the blood of all highly anæmic patients, whether the anæmia was traumatic or essential. True, he distinguishes several varieties of nucleated red blood-corpuscles according to their size,—some uniform with normal red corpuscles, termed by him *normoblasts*, other larger forms called *megaloblasts*, and extremely rare smaller forms, *microblasts*. When, however, he further states that in simple traumatic anæmias it is almost exclusively normoblasts that circulate in the blood, and that in the progressive anæmias, on the contrary, the megaloblasts preponderate, this fact does not afford us any information as to the nature of the essential anæmias, but is only in a measure a fresh sign of the gradually fatal progress of this disease.

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[*] Quincke, 'Volkm. Vortr.,' No. 100; 'D. A. f. klin. Med.,' xx, p. 1; xxv, p. 567; Litten, l. c.

[†] Cohnheim, 'Virch. A.,' lxviii, p. 291; Litten, 'Berl. klin. Woch.,' 1877, No. 19.

[‡] Ehrlich, 'Gesellsch. d. Charité-Aerzte,' 10 Juni, 1880, in 'Berl. klin. Woch.,' 1880, No. 28; Litten, 'Berl. klin. Woch.,' 1880, No. 49.

[§] Eichhorst, 'Med. Ctbl.,' 1876, p. 465; 'Die progressive perniciöse Anämie,' Leipzig, 1878.

Even if you should resort to the clinical course of the malady, the history of the patient, and the anamnesis for aid, you will sometimes find it difficult to decide whether the anæmia should be regarded as secondary or as essential. The course of the process cannot help you to a conclusion, because essential anæmias may be recovered from, and the secondary forms may terminate fatally. Still less can be attained by observation of the patients and by determining the morbid symptoms, presented especially by the vascular system. For the action of both forms of anæmia on the organs, and particularly on the circulation, must necessarily be the same in most respects; so that, ordinarily, the differences occurring in various cases of anæmia are merely differences of degree. With respect to the anamnesis, it is true that in many cases there is no difficulty in discovering the cause of the affection to have been severe hæmorrhage, antecedent tedious and severe pyrexial diseases, or other abnormal blood-consumption or imperfect nutrition, &c.; and in such cases no one will hesitate to regard the anæmia as secondary. On the other hand, we suspect an anæmia to be essential when it has developed insidiously and gradually in individuals who till then have been healthy and robust, its development being due either to no discoverable cause, or, apparently, to the influence of factors which do not generally exert any considerable effect on the blood, such as pregnancy, the puerperal state, and lactation. But, if we wish to be honest, we must ask what is meant by the expression "no cause," and by this reference to factors generally so innocent; do they not amount simply to a confession of our ignorance of the true cause of the anæmia in question? May not the present case have some analogy with that of the idiopathic and deuteropathic cardiac hypertrophies? With the increase of our knowledge the domain of the former has become more and more restricted; who would at present undertake to decide whether a similar fate does not await the essential anæmias? We are already in possession of a communication from Klebs*—a very aphoristic one, it is true,—according to which he found, in a series of cases of pernicious anæmia, the blood presenting minute organisms, identical with those which he had previously observed in scorbutic persons (cf. p. 395), and called by him cercomonas globulus and c. navicula. They were present in such numbers that he felt himself justified in attributing to them a determining influence on the whole disease. He believes that *the cercomonads bring about the disintegration of the blood-corpuscles directly* by breaking them up into larger or smaller fragments, the so-called microcytes. Another possibility is that the prime alteration in many of these anæmias does not first involve the corpuscular elements but the blood-serum, and that, only in consequence of the abnormal composition of the latter do the corpuscles become sympathetically affected. They might then undergo subdivision into fragments of various shapes in a manner similar to that which we know to occur as an effect of high temperatures or induction shocks. This idea, which has been adopted by Ehrlich and others, is at any rate deserving of attention.

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* Ehrlich, "Gesellsch. d. Charité-Aerzte," 10 Juni, 1880, in 'Berl. klin. Woch.,' 1880, No. 28; Litten, 'Berl. klin. Woch.,' 1880, No. 49.

Yet I should be sorry to create the impression that I absolutely disputed the possibility of an essential anæmia. No rational objection could be raised to the application of the term "essential" to those anæmias which, according to Klebs, depend on a direct disintegration of the blood-corpuscles by infective organisms. For if it be a fact that the other organs and tissues do not suffer at all, or are only secondarily affected, it is plain that we are dealing with a blood-disease *in optima forma*. Within the last few years, however, it has become customary to confine the term essential anæmia to those conditions in which we consider there is ground for assuming that the *genesis* of the blood-corpuscles takes place in an imperfect manner, owing to the disturbing influence of some pathological factor or other, *i. e. to diseases of the hæmapoietic organs*. With our knowledge of the subject in this unsatisfactory state you will not be likely to indulge in extravagant expectations; and I willingly confess at the outset that I can offer you no more than a few rough pathologico-anatomical data, which do not allow even of an attempt at explaining and formulating their connection. Some of the experiences in question are pretty old. The name *cachexia s. anæmia splenica* has long been applied to certain chronic anæmias in which, beside the blood-change and certain conditions following and depending on it, the only abnormality found is a *splenic tumor*, whose dimensions are sometimes very considerable. True, the attempt to draw a sharp histological distinction between these and other chronic hyperplasias of the spleen has been hitherto unsuccessful; thus, for instance, the blood-corpuscle-containing cells, which occur in large numbers in the spleen of anæmia splenica, are also found in this organ in leukæmia, fevers, &c. Still we have here a pronounced pathological condition occurring in an organ whose intimate relation to the formation (or destruction) of the blood-corpuscles is established beyond all doubt. To the same category belong, further, certain cases of the *adenia* of Trousseau, Hodgkin's disease, or *pseudoleukæmia*. Some care is, however, called for to avoid placing a false construction on them, till the observed material has been more critically sifted than heretofore. For Virchow* has rightly drawn attention to the fact that there has crept into the literature of the subject a number of cases which must undoubtedly be classed with *lymphosarcomatosis*, *i.e.* a process of tumour-formation which will occupy our attention further on, and to which general anæmia is no more intimately related than it is to every sarcomatosis or carcinosis of equal malignancy. Of the cases remaining after the exclusion of these, some, it seems to me, have a special bearing on the question now before us—cases in which there is found post mortem a widely distributed hyperplasia of the lymphatic glands and follicles, frequently associated with enlargement of the spleen, and abundant cellular infiltration of the hepatic and renal interstitial tissues. The changes are, in fact, identical with those of true leukæmia, though the number of colourless corpuscles contained in the blood is certainly not increased; this fluid having the characters already described as belonging to chronic anæmia.*

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* Klebs, "Art. Flagellata," in Eulenburg's 'Realencyclopädie.'

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* Virchow, 'Geschwülste,' ii, p. 619.

If I do not greatly err, that form of anæmia, which, after the example of Biermer,† is usually called *progressive pernicious anæmia,* also supplies its contingent to the essential anæmias, in the strict sense of the term. Here it is neither the lymphatic glands nor the spleen, but the bone-marrow that is strikingly altered. In a number of the most typical cases of this disease, at any rate, the bone-marrow presents a condition differing conspicuously from the normal; for the usual yellow colour and fatty shimmer, observable as a rule in the medulla of the long bones in adults, is in them replaced by a *dark carmine hue* which to the naked eye exactly reminds one of raspberry jelly. This character is, if possible, still more conspicuous in the spongy bones, so that the medulla throughout the entire skeleton presents the sharpest contrast to the extreme pallor of all the remaining organs and tissues. Since, some years ago, this condition of the bone-marrow was for the first time observed by myself in an exquisite case of pernicious anæmia,‡ it has so frequently been seen by numerous observers in all countries, that its occurrence in this disease cannot possibly be accidental; the only question is as to the nature of the connection. I myself originally thought that special importance should be attached to the nucleated red corpuscles, large numbers of which were present in the red marrow; and this fact has been confirmed by almost all observers. Still their pathogenetic significance for pernicious anæmia has been disputed on the ground that, as you are already aware, the very same nucleated blood-corpuscles are met with in smaller or larger numbers in the bone-marrow in all possible varieties of anæmia. In the most different acute and chronic wasting diseases, such as phthisis, cancer, dysentery, typhoid, they have been found in the medulla by Neumann,[*] Litten and Orth,[†] and others. And since the authors last named have discovered large numbers of nucleated blood-corpuscles in the marrow of old dogs after repeated and copious bleedings, it would appear almost as though no exception could be taken to the view maintained more especially by Neumann, according to which the presence of nucleated blood-cells in the bone-marrow of adults *is the sign and expression of a rapid regeneration of blood-corpuscles*, and consequently in pernicious anæmia also is a mere result of the affection. Still I cannot regard the entire question as settled. The chief difficulty in all examinations of the bones, and more especially in drawing conclusions from experiments, is the fact that an examination of one or several bones affords no sort of guarantee for the condition of the remaining ones. During the course of some experiments carried out by Kraske on dogs in my institute in Breslau, I was able to satisfy myself that the differences in the marrow of the various bones of the skeleton are so great that one is not justified in concluding from the examination, say, of a tibia prior to the withdrawal of blood and of its fellow some time after the withdrawal, that any departure that may happen to be noticed in the condition of the latter is certainly attributable to the blood-loss. But however this may be, if they be right who see in the appearance of nucleated red blood-cells in the marrow and circulating blood, an unequivocal sign of an abnormally increased production of red blood-corpuscles, *i. e.* an effect of the anæmia, still this by no means implies that *all the abnormal properties of the bone-marrow are secondarily conditioned by the anæmia.* The dark-red colour and the richness in nucleated blood-corpuscles, do not, as I may state emphatically, coincide ; rather a dark-red medulla, by no means rich in these cells, is often enough met with, while, on the other hand, large numbers of such corpuscles are often found in much brighter red or even greyish-red marrow. More importance attaches, it seems to me, to the abnormal density of the dark-red medulla, the abnormal richness of which in cells is undoubted, since all the fat-cells have given place to the specific medullary elements. Can it be supposed that such a cellular hyperplasia is really of no importance for the composition of the blood? I am not disposed to assume, however, that the blood acquires the characters of severe anæmia only in consequence of this particular alteration of the medulla. There is no dearth of other pathological appearances. Thus Grawitz* has described several cases of pernicious anæmia, where the post-mortem examination revealed multiple sarcoma-like tumour-formations of the bone-marrow, or a peculiar alteration in which the medulla was almost liquid in consistence, and of a dirty grey colour with portions of greyish yellow interspersed. For these cases—without giving any reasons—he has chosen the name of malignant osteo-myelitis. How much is lacking in all these observations, and how little they are capable of being utilised for a satisfactory scientific explanation of the anæmia, I do not fail to perceive. Still I am unwilling to set a lower value upon them than on the hypertrophy of the spleen and of the lymphatic glands in cachexia splenica and pseudoleukæmia; and taking all in all it may not be hazarding too much if, in addition to the anæmia splenica and the anæmia lymphatica, we establish a third category, the *anæmia medullaris.*

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* Hodgkin, 'Med.-Chir. Transact.,' 1832, xvii, p. 68; Wunderlich, 'A. f. phys. Hlk.,' N. F., ii, p. 123; 'Arch. d. Hlk.,' vii, p. 531; Cohnheim, 'Virch. A.,' xxxiii, p. 451

† Biermer, 'Schweiz. Corr.-Bl.,' ii, No. 1; H. Müller, 'Die progressive perniciöse Anämie,' Zürich, 1877; Gusserow, 'A. f. Gynäk.,' ii, p. 218; Immermann, 'D. A. f. klin. Med.,' xiii, p. 209; Quincke, Litten, Eichhorst, Lépine, l. c.

‡ Cohnheim, 'Virch. A.,' lxviii, p. 291; Litten, 'Berl. klin. Woch.,' 1877, No. 19.

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[*] Neumann, 'Berl. klin. Woch.,' 1877, No. 47; Blechmann, 'A. d. Heilk.,' xix, p. 495.

[†] Litten u. Orth, 'Berl. klin. Woch.,' 1877, No. 51.

But the consideration which, more than all others, weighs with me in making affections of the hæmapoietic organs answerable for the anæmic quality of the blood is the existence of that disease, which, since Virchow[*] described it, has borne the name *leukæmia*. True, it is not usual to discuss leukæmia in connection with the anæmias, for the reason that the poverty of the blood in red corpuscles is completely overshadowed by the *increase in colourless cells*. In leukæmic blood the quantity of white corpuscles is so enormous that the change from an intense red to the colour of chocolate prepared with milk, or in extreme cases even to that of pus, is quite perceptible by the naked eye; while in blood drawn from a vein the proportion of white to red corpuscles is one of the former to twenty or thirty of the latter, and in the severest cases one to two or three. We have, nevertheless, a perfect right to rank this disease with the true anæmias. For no one who has ever examined a drop of such blood under the microscope can have the slightest doubt that in pronounced leukæmia there is not only an increase of colourless cells, but *a very great decrease of red discs*. Even in the milder forms of the disease the same fact has been directly determined,[†] and it is characteristic of true leukæmia, as contrasted with leucocytosis, that the red corpuscles have not simply decreased relatively to the colourless ones, but absolutely. In every attempt to explain leukæmia, both these points must therefore be borne in mind,—the increase of the colourless, and the decrease of the red corpuscles. That the *chemical* examination of leukæmic blood would lead to any special conclusions in this direction could hardly be expected. Substances, absent from normal blood or present in it in smaller quantities, have, it is true, been discovered in the blood and organs of leukæmic patients. Among them are *hypoxanthin* and other *xanthin bodies*, and these substances may be credited with a certain pathognostic significance for this affection,[‡] even when present in the blood only after death and not in the living patient. It is, moreover, very remarkable with what constancy those much-discussed, minute, colourless, but glittering crystals, usually called, after their earliest describer,

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* Grawitz, 'Virch. A.,' lxxvi, p. 353.

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[*] Virchow, 'Ges. Abhandlg.,' p. 147.

[†] Welcker, 'Zeitschr. f. ration. Med.,' 3 Reihe, xx, p. 305.

[‡] Scheerer, 'Verh. d. Würzburg phys.-med. Ges.,' ii, p. 321, vii, p. 123; Salkowski, 'Virch. A.,' l, p. 174, lxxxi, p. 166; Salomon, 'Ztschr. f. phys. Chemie,' ii, p. 65; 'Neue Charité Annalen,' v.

Charcot's crystals, are wont to be deposited, shortly after death from leukæmia, in the blood, bone-marrow, and other tissues. Their chemical constitution has not yet been fully cleared up; K. Huber* believes them to be an unusual form of crystallised *tyrosin;* by others they are supposed to consist of an *albuminoid* or *mucoid* substance. Their source may certainly be sought, with Zenker, in the colourless cells of the leukæmic blood, in the interior or on the surface of which they have frequently been seen by this observer.† These crystals are evidently connected with the richness of the blood in colourless cells, but that the pathogenesis of leukæmia is made no clearer by their presence is sufficiently obvious. The attempt to construe in some measure the genesis of the disease from the morphological composition of the leukæmic blood has also proved abortive. It was supposed that the disproportion between colourless and red corpuscles could be explained by assuming, in addition to an abundant production of colourless cells, either an excessive destruction, or a very much reduced formation, of red ones. In support of the first alternative we were referred to the facts tending to show that a physiological destruction of red corpuscles takes place in the spleen, and it was argued that in the enlarged spleen an unusually large number of red corpuscles are destroyed, owing to a great increase in the cells of its pulp, a view which was supported by the presence of numerous blood-corpuscle-containing and pigmented cells in the leukæmic spleen. But even if we neglect the fact that the discovery of these latter is by no means constant, the lymphatic and myelogenic leukæmias, in which there is often no enlargement of the spleen, manifestly make against the theory. The view according to which chief stress is laid on *the defective new formation of red corpuscles* has for this reason always enjoyed greater popularity. In particular the hypothesis brought forward at the very outset by Virchow, *that leukæmia depends on an imperfect metamorphosis of the colourless into red corpuscles,* appeared to harmonise best with all the facts, so long as this metamorphosis passed current as a physiological postulate.

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* K. Huber, 'A. d. Heilk.,' xviii, p. 485, xix, p. 510.

† For the literature on the subject of Charcot's crystals *vide* Zenker, 'D. A. f. klin. Med.,' xviii, p. 125.

Having only recently discussed the reasons adduced in support of this supposed metamorphosis, and pointed out their inadequacy, it will not be necessary for me to go into the question again, and show how little probability there is for the truth of Virchow's view.

There is not, so far as I see, any other possibility of understanding the constitution of the blood in leukæmia except on the assumption of a *derangement of the functions of the hæmapoietic organs.* Moreover, the results of the anatomical examination of these organs have from the outset called for such an interpretation. In the earliest observed cases of leukæmia it was the *spleen* that, by its enormous enlargement, chiefly attracted attention; somewhat later cases of this disease turned up for examination where, with or without splenic hypertrophy, large numbers of *lymphatic glands* in the most different regions of the body were swollen, sometimes to an almost incredible extent. Accordingly, two forms of leukæmia were distinguished, the *splenic* and the *lymphatic*; and it was considered legitimate to positively diagnose the one form or the other, according to the size of the colourless corpuscles preponderating in the blood. The untenability of this distinction became apparent the moment it was found, through the researches of Neumann, Hoyer, Bizozzero and others, that the bone-marrow takes part in the new formation of colourless blood-corpuscles. Credit is due to Neumann,* above all, for having established, by a number of most careful observations, its important, we may even say preponderating, *rôle*, in the genesis of leukæmia. I, at least, have not during the last few years examined a single case of leukæmia in which I failed to detect the *hyperplasia of the bone-marrow*, recently described by Neumann. This author distinguishes two forms, a *lymphadenoid*, in which the structure of the medulla closely resembles that of adenoid tissue, small lymphoid cells lying closely packed in the meshes of a compact irregularly-shaped reticulum; and a *pyoid*, in which relatively large round-cells fill up wide meshes, which are themselves probably enormously dilated capillaries. The hyperplasia may sometimes be so considerable as to affect the surrounding bone, whose atrophy it then causes. But, though perfectly willing to accept the positive portion of Neumann's work in its entirety, I cannot bring myself to adopt the conclusion at which he has arrived —*that diseases of the bone-marrow constitute the exclusive and sole cause of leukæmia*, while the enlargements of the spleen and lymphatic glands, when present, are mere complications without any importance for the leukæmic quality of the blood. Neumann is certainly quite right when he says that all the older reports of autopsies in which the condition of the bone-marrow is not expressly referred to cannot be utilised in deciding this question. We are, however, in possession of observations of quite recent date, proving that extreme leukæmia has been associated with a medulla on one occasion normal,* on another, not merely not hyperplastic, but even considerably reduced below normal† as the result of an extensive osteosclerotic process. But even were these cases not to hand, it seems to me somewhat extravagant to demand from us that we should deny to an enlargement of the spleen of such extraordinary dimensions as is often seen in leukæmia —and, be it observed, in leukæmia *alone*—any influence on the leukæmic quality of the blood. While we then, as stated, willingly acknowledge the *myelogenic leukæmia* to be the most frequent of all forms, we shall, in my opinion, do well to hold fast the opinion that there occurs in addition a *splenic* and a *lymphatic* leukæmia, and in particular a form dependent on the disease of a combination of these organs.

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* The most detailed account of Neumann's observations is contained in 'Berl. klin. Woch.,' 1879, No. 6 and following; they also contain full references to the literature.

The nature of this disease and the manner in which it influences the blood, causing the latter to acquire leukæmic characters, cannot be satisfactorily explained in the present state of our knowledge. He who deems the known facts sufficiently conclusive to admit of his recognising the spleen, the lymphatic glands, and the bone-marrow as physiological factories for the production of colourless corpuscles will find no difficulty in bringing the increase of the white cells into a direct causal relationship with the hyperplasia of these organs; and the presence of nucleated red blood-corpuscles, so often observed in leukæmic blood, may, similarly, be readily referred to the implication of the bone-marrow. But *pari passu* with the increase in white blood-corpuscles there occurs, as we have emphatically stated, an equally marked *decrease in red ones;* and here the same difficulties crop up as in the other forms of essential anæmia formerly considered. That this is not a mere superficial analogy is indicated with unmistakable clearness by the course of those remarkable cases in which *a pure essential anæmia has preceded the leukæmia* for a longer or shorter period. Litten* has seen in a woman suffering from pernicious anæmia a typical severe leukæmia develop acutely in a few days. In one of the cases described by Fleischer and Penzoldt,† the patient, before becoming leukæmic, presented for a considerable time the picture of an exquisite pseudoleukæmia. Moreover, instances are not uncommon, where the physician has long been obliged to hesitate whether to class an affection with the chronic anæmias or with leukæmia; such cases are to some extent intermediate in their nature. Surely, then, there is no dearth of close relationships between leukæmia and the remaining so-called essential anæmias; but who would venture at present on an exact formulation of these relationships?

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* Fleischer u. Penzoldt, 'D. A. f. klin. Med.,' xxvi, p. 368, 3^{te} Beobachtung.

† Heuck, 'Virch. A.,' lxxviii, p. 475.

While, then, our knowledge, so far as regards the genesis of these diseases, is very imperfect, it is less so when we come to discuss their action on the circulation; it may even be affirmed that an explanation of their symptoms is attended by no difficulty worth mentioning. All individuals suffering from any of these anæmias are *pale*, with a pulse *easily compressible* as a rule, and of low tension. They are predisposed to *hæmorrhages*, and more rarely (never till the later stages of the disease) to œdemas. Among these symptoms, the pallor is the natural result of the reduction in the coloured constituents of the blood—a change, as has been more than once stated, common to all anæmias, however brought about. The alteration in *arterial pressure* is not quite so easily explained. In the case of leukæmia, the idea readily suggests itself, and is positively maintained by many writers, that, owing to the enormous increase of colourless corpuscles, the frictional resistance in the capillaries is greatly intensified, so that, just as in inspissation of the blood, an inadequate supply to the heart from the veins is the result. But whether, if this has any influence at all, it exerts it in the slighter and middle degrees of the disease appears to me rather doubtful; and still less can it be supposed that blood whose corpuscles are reduced in number or contain a smaller amount of colouring matter, though not greatly altered in its remaining constituents, should in any way derange the capillary circulation. Hence another factor deserves, in my opinion, every consideration. A reduction in the number of red corpuscles means a considerable falling off in the number of oxygen-carriers circulating in the blood; and although it cannot be doubted that, in this respect, a certain latitude of accommodation exists, the shortness of breath and muscular feebleness of the anæmic sufficiently clearly proves the limit to be exceeded in the severer grades of the disease. It follows that the *coronary vessels of the heart* are supplied with blood containing less oxygen than is needed for the normal work of the organ, and this cannot occur without lasting prejudice to the energy of the cardiac contractions. But the lowering of arterial pressure is not all; very often the nutrition of the heart and vessels is considerably affected by the defective supply of oxygen. Reserving the more strict demonstration of this connection till we come to discuss the pathology of metabolism, I shall here confine myself to pointing out that one of the first consequences of a lasting reduction of the oxygen-contents of the blood is *fatty degeneration in the vascular system*. In the milder forms, such as chlorosis and leukæmia, only the *intima* of the larger arteries and the *endocardium* undergo the fatty change, but in proportion as the poverty of the blood in functional red corpuscles increases, the vessels become more generally implicated, and, above all, the fatty metamorphosis invades the *myocardium*. Even many of the severe forms of icterus, in which undoubtedly a large number of blood-corpuscles are dissolved, often become complicated by fatty degeneration of the heart. Nor is it uncommon to see marked fatty changes in the heart-muscle of individuals who have become anæmic in consequence of repeated and profuse hæmorrhages, *e. g.* in women with uterine tumours giving rise to frequent metrorrhagia, while an extreme degree of fatty heart is quite typical of so-called pernicious anæmia. That I connect the *tendency to hæmorrhage* with the poverty of the blood in functional red corpuscles you have already learned from our discussion of the hæmorrhagic diathesis (p. 396). The attempt to refer the hæmorrhages of the leukæmic to plugging of the capillaries by colourless blood-corpuscles will meet with but scant approval from you, at least; and it is, in my opinion, rendered valueless by the fact that exactly similar bleedings occur still more commonly in icterus gravis and analogous affections—more especially in pernicious anæmia, whether traumatic or essential. The late appearance of œdema in these diseases is probably dependent on the circumstance that the albuminous contents of the liquor sanguinis remains unaltered, so long, at least, as the digestion and absorption of the food are not interfered with. In the later stages, when hydræmia becomes associated with the anæmia, the setting in of dropsy is no longer deferred.

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* Litten, 'Berl. klin. Woch.,' 1877, No. 19.

† Fleischer u. Penzoldt, l. c.

It only remains, I think, to examine into the effects exerted on the circulation by *foreign corpuscular matters* contained in the blood. In so far as these are bodies having a volume exceeding the diameter of the capillaries, they have been sufficiently discussed in connection with the subject of thrombosis and embolism. For such bodies will naturally be arrested at some point in the vascular system—the smallest not till they have arrived in the most minute capillaries—and will now, according to their nature, manifest their presence either by their purely mechanical effects or by their action as specifically infective emboli. That inflammation, hæmorrhage, or necrosis, or a combination of these processes sets in in the vicinity of the infective plugs has been stated more than once, and of this I shall have again to speak when dealing with necrosis. But foreign bodies so small as to pass freely through even the finest capillaries demand a brief notice. This question is far from unimportant from a patho-ogical standpoint. Passing over the microscopic round-orms, not very uncommon in the blood of living animals, *e. g.* the raven and, in many districts, the dog, we have numerous reports from tropical countries as to the presence of microscopic *filariæ* in human blood, *Filaria sanguinolenta* and *Filaria sanguinis hominis*. The latter of these is regarded by its discoverer, Lewis,* as the cause of chyluria—a subject which will be discussed later on. But much greater significance attaches to this question on considering it from another point of view. For if the parasitic theory of infective diseases is really well established, the fate and effects of these *most minute corpuscular beings* after having gained an entrance to the circulation must excite intense interest. Yet this reference to the infective diseases will at once show you how very meagre is our knowledge of the point under discussion. Only in cases where an abraded surface or an ulcer is present do we know the path by which the *lowly organisms* or their spores enter the vessels. In the vast majority of infective diseases we are far from being able at present to specify their place of entrance, and are obliged to rely on guesses, or, at best, on the analogies offered by the solid particles which, either mingled with the inspired air, penetrate the pulmonary lymphatics, or with the food, enter the chyle-vessels. There is no doubt that when *schizomycetes* have arrived in the vascular system they can there *multiply* to an extraordinary degree, as has been positively shown to be the case with the bacteridia of splenic fever. As to the effect exerted on the animal-organism by their admixture with the blood no general rule can be laid down; it is different in splenic fever, in relapsing fever, in smallpox, &c. But even if we confine our attention to the vascular system alone, we find that, during the febrile attack in relapsing fever, incredible numbers of spirilla circulate in the blood for several days together, apparently without causing the slightest disturbance of the circulation or alteration in the heart and vessels; while the multiple hæmorrhages observed in typhus, in the skin, muscles, and other parts, clearly point to *impairment of the vessel walls*—a conclusion which is supported in no small measure by the hæmorrhagic variety of smallpox. If, however, the statements of Klebs be correct, the disintegration and destruction of numbers of red corpuscles may be the direct consequence of the presence of parasitic organisms in the blood. When we ask, in conclusion, what becomes of the schizomycetes when the individual survives the attack, the answer is also doubtful enough. Very often they disappear completely from the vessels. That this is owing to their direct destruction in the circulating blood is in itself quite possible, though we have no positive proof of its occurrence. It is certain, on the other hand, that they may be *excreted* from the blood. This can be very beautifully seen in the kidneys of guinea-pigs or rabbits which have died of splenic fever; here it is not uncommon to find some of the bacilli within the loops of the glomeruli, and some outside these, but still within the capsule of Bowman, or they may already have entered the lumen of the uriniferous tubules. In many infective diseases, moreover, there are present in the kidneys small foci of disease whose centre is formed by a colony of bacteria situated in the interior of a uriniferous tubule; and I can only account for them by supposing an *excretion of micrococci* into the urinary passages and a secondary development there into colonies. The third and perhaps commonest modus by which the schizomycetes are removed from the vascular system is their *appropriation by the cells* of the same organs that take up and retain granular colouring matters introduced into the blood; these organs are the spleen, the liver, and the bone-marrow, but more especially the first named. Of the spleen, in particular, it is established that after the injection of micrococci into the blood or abdominal cavity colonies may always be discovered in its pulp, and it is quite impossible to say at present how many single micrococci are taken up by the cells of the spleen and bone-marrow. The highly characteristic bacteridia of anthrax have often been seen in the interior of the splenic cells,* and Sokoloff† has gone so far as to declare that in his opinion the splenic tumor of infective disease is called forth by the lodgment of schizomycetes in the tissues of the organ. As regards the spirilla of relapsing fever, it is most probable that their spores at least are deposited somewhere in the organism during the pause, and that from them is developed the new generation which excites the second attack. But the micrococci do not always disappear from the vascular system in this more or less direct manner. If they be such schizomycetes as gradually multiply to form heaps and colonies, it not infrequently happens that the latter develop in the blood itself and become specific emboli in the capillaries of the coronary vessels of the heart, in the renal and cerebral vessels, as well as in those of other localities. It is possible too, that *ulcerative endocarditis* originates in the same manner, the bacteria having developed into colonies in the blood and then settled on the valves of the heart. Lastly, if the hypothesis, already enunciated, of the parasitic origin of infective inflammations be correct, it implies that the schizomycetes forsake the vascular system only to give rise to inflammatory disturbances of the circulation in some organ, where the soil is favorable to their development.

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* Lewis, "On a Hæmatozoon inhabiting Human Blood, &c.," Calcutta, 1872, 'Lancet,' 1875, i, p. 209; 'Med. Times and Gazette,' 1875, Feb. 13, p. 173.

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* Koch, in F Cohn's 'Beiträge z. Biol. d. Pflanz.,' i, Heft 3, p. 277.

† Sokoloff, 'Virch. A.,' lxvi, p. 171.

While then it is true that in this domain also we can barely do more than formulate the problem for the solution of which many details are still wanting, no small share of the blame for this state of things is attributable to the extraordinary difficulty of becoming acquainted with and tracing most of the schizomycetes by means of our present optical and chemical aids. The task is far easier of accomplishment in the case of the more highly organised hyphomycetæ, which are all of larger size, and whose developmental forms are better known. Hence, when we consider the enormous distribution of the common mould-fungi, it is not surprising that their behaviour on being introduced into the juices of the body should have been earlier brought to the test of experiment than was that of the bacteria—even though there were no definite pathological data to suggest such a course. Passing by older experiments, we may mention a communication of Grohé,* which though it was and remains very fragmentary created a great sensation at the time of its appearance. This writer had succeeded in producing, by the injection of the spores of the *Penicillium* and *Aspergillus glaucus* into the blood of rabbits and dogs, an acute and fatal growth of hyphomycetæ involving all the internal organs. Yet although Grohé's experiment has often been repeated during the ten years following its publication, no one ever obtained the results reported by him. On the contrary, the conviction gained ground that the spores of the common moulds when injected into the blood are in part excreted by the kidneys with the urine and in part dissolved in the circulating blood, whence they disappear in a short time.* This want of success caused the observations of Grohé to be so far forgotten that Naegeli formulated the law—the hyphomycetæ, in contrast to the schizomycetes, cannot thrive in the interior of the body;† while Grawitz, who as a pathologist was accustomed to a more cautious mode of thinking and speaking, set himself to discover the conditions inimical to the germination and development of the moulds in the interior of the animal organism. Nevertheless the positive experiments of Grohé could not thus be finally disposed of, and, moreover, additional facts became known, all pointing to the need for caution before coming to a conclusion. Thus Wreden‡ convinced himself that, while in *myringomycosis* the formation of hyphomycetæ was as a rule confined to the epidermis, in exceptional cases the aspergillus penetrated the deeper layers of the tympanic membrane, and even caused its perforation. Still more worthy of notice was the observation made by Leber§ of a case of hypopion-keratitis which depended on the growth of aspergillus—a discovery which led him to undertake successful inoculation experiments on the eyes of rabbits. Quite recently the entire question has taken a turn—at first sight very surprising—owing to the highly interesting researches of Grawitz.‖ In undertaking the task of experimentally testing the value of those conditions, which were supposed by him to act as a check to the development of the mould-fungi in the animal body, it was of course impossible to alter the characters of the animal organisation.

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* Grohé, 'Berl. klin. Woch.,' 1870, No. 1; A. Block, 'Beiträge z. Kenntniss d. Pilzbildung in den Geweben d. thierischen Organismus,' I.-D. Stettin, 1870.

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* Grawitz, 'Virch. A.,' lxx, p. 515.

† Naegeli, 'Die niederen Pilze,' München, 1877, p. 38.

‡ Wreden, 'A. f. Augen-u. Ohrenheilk.,' iii, 2, p. 56, 1874.

§ Leber, 'A. f. Ophthalm.,' xxv, 2, p. 285.

‖ Grawitz, 'Virch. A.,' lxxxi, p. 355.

He therefore attempted to accustom the hyphomycetæ, which usually vegetate on an acid, solid substratum at from 10—20° C., to the unfavorable environment of the animal body, *i. e.* to a liquid, alkaline medium, having a temperature of about 39° C.; and to accomplish this he adopted the method of gradual cultivation extending over many generations. In fact, by gradually altering the external conditions, he finally succeeded in cultivating any mould in neutral and then alkaline solutions of albumen at the temperature of the blood; and in this way he obtained varieties of penicillium and aspergillus which, though *morphologically* unaltered, not only throve in warm alkaline nutritive fluids, but were able to compete successfully with the bacteria. When he now injected this variety into the blood of living animals, innumerable foci of mould-vegetation were very rapidly developed in almost all the organs; to these rabbits succumbed after, on the average, eighty, and dogs after the lapse of about one hundred, hours. When intra-jugular injection is employed, the first foci recognisable to the naked eye make their appearance in the lungs and kidneys, the latter of which continue to be the most strongly affected organs; after these the most numerous foci are found in the liver, intestines, and muscles, while the spleen, bone-marrow, lymphatic glands, skin, and nervous system are only very slightly involved. On injection into the carotid, on the other hand, it is the brain and retina that chiefly suffer. Less danger attended the introduction of the spores into the abdominal cavity; in this case only a few examples escaped into the blood, and germinated in the ordinary way in the organs, while by far the greater number were arrested in the peritoneal lymphatics, and here produced mycotic foci. The results were still less severe, being completely localised, after injection into the subcutaneous tissues and inhalation into the lungs. The germination of the individual spores takes place in the ordinary manner; the foci in the various organs, which to the naked eye resemble tubercles in many respects, are similar in size and other particulars to the clumps of hyphomycetæ cultivated on any nutritive material one may select—with a single and really notable exception that *they form only rudimentary fruit-receptacles and never reach the stage of spore-*

abstriction, without doubt owing to the absence of free oxygen. Hence it follows that the spores germinate and sprout, but do not multiply. In view, however, of the capacity possessed by them of forming enormous ramifications and producing hyphæ this can hardly interfere with their wide distribution throughout the body. In the experiments of Grawitz, it is true, the quantity of spores injected and the particular foci of disease so originated in organs of vital importance were the chief sources of danger to the animal; there was no sign whatever of septic blood-poisoning or other general pyrexial disease.

You will of course think me justified in thus minutely dwelling on the experiments of Grawitz. The principle underlying them would be of very far-reaching importance, could we accept without reserve the conclusions arrived at by the author. But while fully acknowledging the happiness of the conception on which the series of experiments is based, as well as the elegance of the methods employed, I am, nevertheless, not fully convinced that the positive results were attained by modification of the hyphomycetæ through cultivation. That there exist—even if we ignore myringitis and keratitis aspergillina—varieties of mould-fungi capable of thriving in the living animal body is established beyond all doubt by the observations of Grohe,* and who will guarantee that in Grawitz' successful experiments "accident" had not thrown in his way a variety of aspergillus capable of development? If this were so, the experiences of Grawitz would lose a great part of their theoretic interest. In any case, however, they are sufficiently worthy of attention, although a somewhat more accurate description of the action of the hyphomycetæ-foci on the tissues in their immediate vicinity would have been very welcome to many persons. But whatever may have been the circumstances to which the positive results of those experiments were due, we may conclude from the present state of the entire question that there is no reason for entertaining serious apprehensions of an invasion of the human body by hyphomycetæ. For not merely can no actual danger arise from them except where they have effected a direct entrance into the vascular system, but it is only in very exceptional cases that the mould-fungi are capable of vegetating and thriving in the juices of the animal body. Hence, while the possibility of such an unfortunate accident—the coincidence of both these conditions—cannot be denied, to the practical pathologist the history of the common mould-fungi will rather serve as instructive evidence of the degree to which the living animal organism is capable of resisting widely disseminated and active noxæ.*

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* Not long ago Lichtheim also showed me preparations of fungus germination and growth in the kidneys of rabbits, where the spores had obtained access through manipulations carried out on the ureter.

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* On the subject of Chronic Anæmias consult further Wagner, 'Hdb.,' p. 706; Immermann, in 'Ziemssen's Hdb.,' xiii, 1, p. 272.

CHAPTER X.

PATHOLOGY OF THE LYMPH-STREAM. DROPSY.

Conditions necessary to the normal flow. Lymphangitis and lymph-thrombosis.—Solutions of continuity of the walls of the lymphatics.—Lymphorrhagia.—Chylous ascites and hydrothorax.—Impediments to the flow of lymph due to weakening of the motor forces, and to the interpolation of abnormal resistances in the lymph-channel.—Occlusion of the thoracic duct.

Dropsy is invariably a consequence of increased transudation.—Want of uniformity in the behaviour of the blood-vessels with respect to transudation.—Hydrops mechanicus.—Its theory.—Dropsy due to increased permeability of the walls of the blood-vessels.—Hyd. inflammatorius.—Hyd. cachecticus.

Nervous œdemas.—Pulmonary œdema.

As we now, at the conclusion of our studies on the pathology of the circulation, turn our attention to the pathological events occurring in the lymph-stream, will you from the outset bear in mind *that all lymph has its source in transudation from the blood-vessels?* True, the lymph which we collect from the lymphatics is not the pure transudation that exudes from the capillaries; for it contains the products of the metabolism of the organs and tissues in which the particular lymphatics have their origin. Hence it is obvious that morbid disturbances of the condition or function of the individual organs must exert an influence on the composition of their lymph, and we shall further on have many opportunities of noticing alterations of this kind. Here, where we are dealing with the general pathology of the lymph-stream, we may omit the consideration of this factor, more especially as the changes affect only the so-called extractives, and therefore cause no alteration in the amount or concentration of the lymph, nor, consequently, in its flow.

In order that the flow of lymph may take place in a regular manner it is necessary above all that there should be a normal transudation from the vessels. We have already cited examples which demonstrate *the immediate dependency of the lymph-stream on the transudation.* In venous hyperæmia the increased transudation was immediately followed by an increase of the lymph-stream, and in inflammation the same thing was apparent; on the other hand, the lymph-stream dries up when the transudation ceases or is reduced to a minimum through arterial ischæmia. But, as is well known, the transudation is not merely the source of the lymph, but also the *cause of its flow through the lymphatics.* Certain genera of animals possess a lymph-heart; and in the mesenteric chyle-vessels of the guinea-pig Heller* saw *rhythmical contractions.* With respect to the remaining mammals, and in particular man, nothing is known of such a motor-mechanism in the lymphatics; in them the only known force engaged in the propulsion of the lymph is *the difference between the tensions at the commencement and at the termination of the lymphatics, i. e.* the difference between the pressure under which the transudation is poured out into the interstices of the tissues and that prevailing at the point of entrance of the ductus thoracicus into the v. subclavia. In addition there are, as you are aware, certain accessory forces—the muscular contractions, the diastolic suction-action of the heart, and the similar action of the thorax during inspiration. Nothing is known of any independent co-operating action on the part of the lymphatics themselves. The various lymph-streams all pass through some of the lymphatic glands on their journey; and here without doubt they receive a considerable number of lymph-corpuscles. It has not yet been made out whether the latter are one and all produced in the lymphatic glands, or whether some of them are colourless corpuscles that have emigrated from the vessels in the interior of the glands. That there is good reason to regard the *transudations of the*

* Heller, 'Med. Ctbl.,' 1869, p. 545.

cavities as analogous to the lymph of the parenchyma, you know from your physiological studies. The serous cavities are, as it were, colossal lymph-spaces having an endothelium endowed with the same power of preventing the coagulation of the lymph as is possessed by that of the lymphatics proper. This *power of checking coagulation* must exist, since lymph when removed from the lymphatic vessels and serous cavities is wont to coagulate sooner or later. But it need not be nearly so marked as it is in the walls of blood-vessels, inasmuch as the coagulability of normal lymph and serous transudations is very considerably less than that of the blood. Hence the coagulation of the blood on escaping into the pericardium is not surprising, nor is there anything remarkable in the fact that inflammatory transudations, with their exalted coagulability, should so readily deposit pseudo-membranes on the serous surfaces particularly; though in the latter case it is possible that more or less extensive defects in the endothelium may exert an important influence.

Let us suppose the transudation from the blood-vessels to be normal in constitution and amount, and a perfectly standard lymph to be present in the commencements of the lymphatics, the question arises whether this lymph can undergo *pathological alterations of composition* on its further journey, and whether its *forward movement*, *i. e.* the lymph-stream, can experience *any kind of disturbance*. That everything entering the lymphatic stream, whether accidentally or intentionally introduced, is swept away by the lymph, and thus alters its composition, is so apparent as to need no proof. If a solution of morphia be injected under the skin, the lymph of the vessels in question contains morphia; after every fracture of bone there are drops of liquid fat in the lymphatics of the part; after every subcutaneous extravasation a multitude of red corpuscles, and after tattooing granules of vermilion or Indian ink. All these substances are transported at least as far as the nearest lymphatic glands; many of them pass through these, but others are here deposited, either permanently or till they become gradually disintegrated, according to the nature of the materials. If we except foreign contamination, it is clear that the constitution of the lymph can only be altered by morbid processes in the lymphatic glands or lymphatic vessels. How very meagre our knowledge is with regard to the pathology of the lymphatic glands I was quite recently obliged to confess to you. We are in possession of only a single fact derived from experiment,—that a concentrated lymph, rich in corpuscles, flows from inflamed glands;* and as for pathological experience, it is, as you know, highly probable, though by no means certainly established, that the v. efferentia are the agents by which the abnormally abundant supply of colourless corpuscles from leukæmic lymphatic glands to the blood is effected. We are, moreover, utterly ignorant of the constitution of the lymph which flows from caseous glands, and the same remark holds good of all the remaining morbid processes in which the lymphatic glands are implicated. Turning to the lymphatic vessels you will no doubt at once think of *lymphangitis*. But though the name is very commonly used, it is not strictly speaking applicable. For in the vast majority of these cases the inflammation involves the sheath of the lymphatics and surrounding connective tissue rather than the vessels themselves. The starting-point of the lymphangitis is mostly an infective inflammatory focus, and the ensuing phenomena are nothing more or less than evidences that the phlogogenic agent is creeping along the course of the lymphatics and exciting inflammation wherever it arrives. I do not, of course, deny that the walls of those lymphatics which possess proper blood-vessels, *vasa sanguinea vasorum lymphaticorum*, are involved in these inflammations. But the quality of the lymph which flows through the lumen of such inflamed vessels can be no more influenced by this process than is the composition of the venous blood by phlebitis. The inflammation assumes importance only when the vessel wall suppurates, when the intima or the endothelium is detached, when, in short, the vessel is so affected as to lose its power of preventing coagulation. The natural result is then a formation of lymph-thrombi, which are the more certainly developed as the lymph in such cases is inflammatory, *i. e.* a very readily coagulable one. The thrombosis is still more rapid when the walls of the lymphatic vessels are *necrosed*. Other morbid processes, such as are met with in the blood-vessels, *e. g.*

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* Lassar, 'Virch. A.,' lxix, p. 516.

amyloid degeneration, sclerosis, &c., do not occur in the lymphatics. If you ask what importance is to be attached to lymph-thrombosis, the reply is that, so far as the lymph-stream itself is concerned, the mechanical factor alone is important; by the coagulation there is introduced into the course of the lymphatics an abnormal resistance which must be regarded as the equivalent of occlusion of the vessel, provided that, as is usual, the thrombus is an obstructive one.

This brings us to the second point—the casual disturbances to which the flow of lymph is open. The lymph is diverted from its natural channel when the walls of the lymphatics have undergone a solution of continuity. Lymph may escape from the peripheral lymphatics, more especially of the extremities, or from the ductus thoracicus—in both cases in consequence of injury. Yet peripheral *lymph-fistulæ* due to ulcerative processes have also been met with, and rupture of the thoracic duct after enormous dilatation in consequence of stenosis has been several times observed. The lymph escaping from an opening in the affected vessel is under all circumstances lost to the lymph-stream, and hence to the blood-circulation; yet the effect so produced is by no means proportional in all cases to the amount of lymph lost. A peripheral *lymphorragia* is always much less hazardous than is one from the d. thoracicus. For in the latter case not only is the chyle completely or partially removed, but even in *fasting* animals the lymph of the trunk appears to possess a greater dignity *quoad vitam* than does that of the extremities. Lesser,* experimenting in Ludwig's laboratory, found that in fasting animals no bad results attend the withdrawal of a very considerable amount of lymph from a fistula of the thoracic duct, provided that pumping movements be carried out on the extremities; whereas, if the extremities remain at rest the animals die after a loss of lymph equal to less than a fourth part the blood-quantum. The other results of lymphorrhagia depend chiefly on the direction in which the extravasating lymph is poured out. In peripheral lymph-fistulæ it is invariably discharged *on to the surface of the body*. This has also been observed in injury of the thoracic duct, although in these cases as a rule, and certainly in ruptures of the duct, the contents of the latter enter the corresponding serous cavity. In this way there originate *chylous ascites* and *chylous hydrothorax*,* whose amount is generally very considerable, and which have obviously a tendency to be very rapidly renewed after tapping. If the solution of continuity of the duct be due to rupture in consequence of abnormal distention, recovery is probably impossible. On the contrary, after wounds the process of healing is as a rule easy of accomplishment, since the trifling pressure under which the lymph everywhere flows essentially favours the adhesion of the edges of the wound and its spontaneous closure by thrombosis.

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* Lesser, 'Arb. aus d. Leipz. phys. Anst.,' 1872.

Under these circumstances a greater interest attaches to the subject of the slowing and obstruction of the lymph-stream, whether this be due to a *falling off in the motor forces* or to the *interpolation of abnormal resistances*. But can the lymph-stream really be impeded by the former of these causes? The motor force chiefly instrumental in carrying on the circulation of the lymph is, you are aware, the transudation through the vessel walls; and, as already stated, we are not acquainted with any active co-operation on the part of the lymphatic vessels. Hence so-called *paralysis* of the lymphatics, which is sometimes looked upon as the cause of various dilatations of the lymphatic spaces, cannot be seriously discussed in this connection. The only point we have to consider is, in my opinion, how the lymph-stream reacts when the action of the well-known *co-operating forces* is suspended —when, as may happen, the muscular movements are reduced to a minimum, and the inspiratory suction-action of the thorax is considerably impaired by shallow respirations, or still more by emphysema and the like. Now will you please bear in mind that the production of lymph in the extremities *itself* becomes extremely scanty in the absence of muscular movements, and that, although the inspiratory suction-action of the thorax should cease, there still remains a corresponding action of the heart in diastole. That aspiration by the thorax is far from necessary to the regular continuance of the lymph-stream is most clearly taught by the behaviour of the latter in a curarised dog whose respiration is maintained artificially. If a dog be treated in this way and the d. thoracicus exposed where it enters the subclavian vein, you can see through the thin wall of the vessel the continuous flow—strengthened only at each diastole—of the lymph as it enters; and this is observable even when the peritoneal cavity is laid open, and consequently in the absence of any pressure by the abdominal muscles. Accordingly, I think we may unhesitatingly infer that, so long as the production of lymph does not exceed the normal limits, *absence of the oft-mentioned accessory forces is incapable of leading to any disturbance of the lymph-stream worth mentioning.*

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* Cf. Quincke, 'D. A. f. klin. Med.,' xvi, p. 121 : also contains references to literature.

The *interpolation of abnormal resistances* in the course of the lymphatics must, on the other hand, impede the lymph-stream in a very much higher degree. In the peripheral lymphatics the resistance may be occasioned in various ways, and in the lymphatic glands the stream is equally liable to meet with more or less powerful impediments. You will, however, gladly dispense with apposite illustrations on hearing that even *the complete interruption* of the lymphatic stream by the application of a ligature is *practically unattended by consequences.* You may fully extirpate the lymphatic glands from the popliteal space of a dog—the large glands which receive the principal lymphatic trunks from below the knee—without giving rise to any morbid symptoms in the paws or legs, and, in particular, without any trace of œdema. It is easy to explain why this is possible. By means of the very large number of lymphatic vessels undergoing repeated anastomosis, and capable, therefore, of representing one another, provision is made that the occlusion of one or even more lymphatics shall be followed by no disturbance in the return of lymph; while as regards the lymphatic glands their anatomical arrangement is such that the lymphatics of an area do not all enter *the same* glands, a number of branches passing by these and discharging into those situated next above. Thus in a dog whose glandula poplitea have been shut off by a ligature, the inguinal or pelvic lymphatic glands may be readily injected from the hind paw.* Finally, when through some cause or other the *whole* of the lymphatics leading from a part have actually been rendered impervious, the blood-capillaries, as a last resource, can take on their function vicariously by themselves undertaking the removal of the parenchymatous fluids, till through the establishment of anastomoses with the lymphatics of the neighbourhood *new lymphatic effluents* have originated. Even when the d. thoracicus has become occluded in man, either by tumours, by a cicatrix, or by thrombosis of the v. subclavia, a development of collateral effluents has been repeatedly noticed; and when the d. thoracicus of a dog is ligatured at its termination the consequences which would otherwise attend the operation are almost invariably compensated in this way. Should this collateral circulation fail to be developed, then, indeed, the result is wide-spread stagnation, chiefly of the chyle, and, to a much slighter extent, of the lymph throughout the entire body. The duct itself on the peripheral side of the obstacle as well as the cysterna chyli and chyle-vessels of the mesentery become distended into *thick varicose cords*. The lymphatics of the liver and kidneys are also conspicuously wide, while an abnormal dilatation of the peripheral vessels has not been observed except in isolated cases. That the strongly distended chyle-vessels occasionally rupture I mentioned a few moments ago. But even if we disregard the chylous ascites thus originated, the consequence of stenosis and occlusion of the ductus thoracicus, when no collateral channels come to its aid, is always hydrops—ascites and probably œdema of the abdominal organs. The condition of the skin and extremities cannot be gathered with any certainty from the literature; general œdema or extensive scleroderma is often mentioned as due to imperviousness of the thoracic duct, although in other cases special stress has been laid on the absence of dropsy, and this by eminent authorities.* The difficulty of coming to a decision on this point is still further increased by the fact that many of the examples of closure of the duct were complicated by a constitutional disease which in itself tended to produce dropsy, *e.g.* where the occlusion was due to metastatic cancerous nodules. This applies with special force to that variety of impediment which is indisputably the most frequent of all those to be overcome by the lymph-stream of the ductus thoracicus, namely, the increase of venous tension produced by non-compensated or imperfectly compensated cardiac lesions. That the entrance of the chyle into the subclavian vein must in such case be essentially impeded goes without saying; but at the same time you are aware that this factor is not necessary to an explanation of the dropsy of persons suffering from heart disease. But however this may be, will you, at any rate, bear in mind, that the whole question of dropsy through interference with absorption and with the lymph-stream applies only to abnormal resistances in the ductus thoracicus? Even *total occlusion* of all the lymphatics of a part is never followed by œdema of the part provided the secretion of lymph within it is normal. For the extremities this fact has been indubitably established by experiment and by pathological experience; hence it appears to me extremely hazardous to assume with Wegner* for the abdominal cavity that diminished resorption by the diaphragmatic pump is a direct cause of ascites. Even did the resorption by the lymphatics of the diaphragm cease completely, the blood-vessels of the peritoneum would suffice to carry off the small quantity of peritoneal fluid which must in a normal condition be absorbed in order that the continuous renewal of the serous transudation may be carried on. All these considerations lead, you see, to but one conclusion, *namely, that for the production of hydrops the transudation from the blood, i.e. the lymph-formation, must be increased above the normal.* There is a very substantial reason why the whole question of œdema should centre round this point. For if it be due to the vicarious action of the blood-vessels that cessation of resorption by way of the lymphatics causes no abnormal accumulation of fluids in the parenchymatous organs or body cavities, it immediately follows that every disturbance affecting the resorptive power of the blood-capillaries must much more certainly lead to œdema than does disturbance of the lymphatics; but that these processes precisely which so powerfully augment the transudation from within outwards (the filtration) must directly impede the flow in an opposite direction is at once obvious. Accordingly whenever we meet with an œdema or hydrops we shall always ask ourselves the question, *what is the cause of the pathological increase of the transudation* from the vessels of the part affected? For in the vast majority of all dropsies we shall find the lymphatic stream not merely not impeded but even accelerated and augmented—in all cases, at least, where no additional special obstacle is opposed to it. But if an abnormally copious transudation be in itself capable of causing œdema, despite the perviousness of the lymphatics and augmentation of the flow of lymph, it is self-evident that the rapidity with which the œdema develops and the dimensions attained by it will increase in proportion to the smallness of the quantity of fluid conveyed out of the part by the lymphatics. The final conclusion to which we are led by our discussion is,—*interference with or stoppage of the lymph-stream cannot, it is true, give rise to œdema but can increase an œdema otherwise conditioned.*

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* According to unpublished experiments carried out by v. Schulthess-Rechberg in the Pathological Institute of Leipsig.

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* Cf. Virchow, 'Hdb.,' i, p. 202; further, Heller, 'D. A. f. klin. Med.,' x, p. 141.

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* Wegner, 'Langb. A.,' xx, p. 51.

The conditions under which the transudation from the blood-vessels is abnormally increased have already been so thoroughly discussed that we can here afford to dispense with a consideration of them. The first, and certainly not the least, difficulty in the whole matter arises out of the circumstance that the behaviour of the vessels with respect to transudation is not the same throughout the whole of the body. As regards the abdominal vessels there were a number of facts pointing to a peculiarity in the constitution of their walls. According to an oft-quoted experiment of Herbst,* which Brücke† was repeatedly successful in confirming, when milk is introduced into the jugular vein of a dog its globules pass over into the liver and other abdominal organs. An analogous occurrence was observed by Toldt‡ on injecting aniline-blue into the vascular system of a dog; and I have more than once mentioned that during digestion the chyle-vessels of the mesentery constantly contain a number of red blood-corpuscles. To these facts must be added the results of the experiment on hydræmic plethora,§ which show in the most striking way that the vessels, not only of the abdominal organs, but of all organs whose function consists in the separation of a watery secretion, possess a degree of permeability to water and watery solutions very different from that of the vessels throughout the remainder of the body. I lately called your attention to the naturalness of assuming that this property of the vessel walls is connected with the secretory functions of the organs in question. To say more than this would not, so far as I can judge, be justifiable in the present state of our knowledge. We must first have an exact acquaintance with the individual component parts and stages of the process of secretion. So long as we are denied an insight into the finer mechanism, by means of which the same arterial congestion is unaccompanied by the slightest trace of transudation in the absence of excitation of the secretory nerves,* and at other times, when it coincides with the activity of these nerves, permits such an abundant passage of fluid—so long, I say, shall we in vain attempt to explain the behaviour of the gland-vessels towards an augmentation of the absolute watery contents of the blood. To simply lay it down that these organs are originally set apart as regulators of the quantity and quality of the blood by securing the removal from the vascular system of everything foreign to it, would in the first place be a paraphrase and no explanation, and would in the second place leave the real difficulty untouched. For this consists in the fact that in hydræmic plethora the vessels concerned allow the passage of the fluid *quite independently of the action of the secretory nerves*; so that in a dog, the function of whose chorda is completely suspended by atropine, the salivary glands become highly œdematous after salt solution has been injected into the blood. But since we are here face to face with an unsolved enigma, it is the more matter for congratulation that precisely these œdemas of hydræmic plethora have no *practical* significance, if I may use the expression, inasmuch as they can hardly occur in human pathology.

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* Herbst, 'D. Lymphgefässsystem u. s. Verrichtung.'

† Brücke, 'Vorl. über Physiol.,' 2 Aufl., 1875, i, p. 202.

‡ Toldt, 'Wien. akad. Stzgsb.,' lvii, Abth. 2, 1868, Febr.

§ Cohnheim u. Lichtheim, 'Virch. A.,' lxix, p. 106.

The œdemas with which the latter has to reckon are limited to two varieties—that depending on *venous stagnation* and that due to *alterations in the vessel walls*. You have learned from former lectures what an important part is played in pathology by œdema of the first category. General stagnative, or as it is termed, *mechanical* dropsy as well as dropsies of particular parts are some of the most common everyday experiences; the former, *e.g.* in imperfectly compensated cardiac lesions, the latter in venous thrombosis and all kinds of processes which raise the pressure on the venous side. I then attempted to show, too, that the factor which essentially determines the onset of the dropsy is the disproportion between afflux and efflux, and that the occurrence of mechanical œdema after paralysis of the vaso-motors in circumstances where, as demonstrated by Ranvier,* without paralysis it would be absent, depends solely on an increase of this disproportion. Moreover, this proof of Ranvier has, for reasons easily understood, impressed physiologists and histologists more than it has pathologists. On now inquiring into the finer mechanism of mechanical hydrops we shall naturally think first of the *augmentation of pressure* in the capillaries which must necessarily follow on venous stagnation. But although the pressure is without doubt one of the determining factors in the process of filtration, it may be directly proved that the walls of the blood-vessels, as compared with ordinary physical membranes, react differently to changes of pressure. For if, *cæteris paribus*, the transudation through the capillaries increased proportionately, or nearly so, to the internal pressure, it would be impossible to discover why arterial congestion—which undoubtedly raises the capillary pressure, though to a less degree than does venous stagnation—is absolutely without influence on the transudation of the part affected. This is, however, the case, not only in the skin and muscles but in the glands also. On producing paralysis of the secretory nerves of the submaxillary of a dog with atropine, and stimulating the chorda, there follows, as was shown by Heidenhain,† a most typical arterial congestion of the gland; yet *not a drop more lymph* flows from a cannula fixed in the cervical lymphatic trunk than there did before the stimulation. In only one locality does œdema arise in consequence of arterial congestion; this is the tongue of the dog, which, as you saw yourselves, swelled on prolonged irritation of the lingualis (p. 141). But however indubitable this fact, it remains up to the present an isolated one, so that, owing to its exceptional position, no conclusion of a more general kind can be drawn from it. So long, in particular, as the details of the process by which the tumefaction is here brought about continue unknown, the rule, established by various experiments in the most different localities, that arterial fluxion causes no perceptible increase of transudation, must retain its full validity. But apart from the amount of the rise of pressure, let us consider in what other respect the circulation differs in capillaries which are the seats of congestion and of stagnation; the *velocity* of the blood-stream is altered, being in the one case considerably increased, in the other no less diminished. In that form of retardation of the flow which sets in in the train of local anæmia, the transudation undergoes, it is true, no increase whatever; but here the capillary pressure is not only not augmented, but even reduced below normal; and hence this fact in no way prejudices the possibility that with the increase of pressure a retardation of the stream must be associated before the filtration through the blood-vessels can exceed the normal. The second and much more striking contradiction between the laws of capillary transudation and those of filtration through physical membranes is apparently disposed of by the recent investigation of Runeberg* on the filtration of solutions of albumen. For while it was formerly generally held that the quantity of albuminates filtering through a membrane was greater the higher the pressure under which filtration took place, this writer has determined by experiments in which he employed fresh rabbit's intestine for his filters *that, other conditions being equal, less albumen filters through the higher the filtration-pressure becomes.* No doubt the identification of the rabbit's intestine with the living capillary wall is in many respects a doubtful proceeding; moreover, the experimental results of Runeberg have by no means passed undisputed.† However this may be,

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* Heidenhain, 'Pflüg. A.,' v, p. 309.

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* Ranvier, 'Compt. rend.,' lxix, No. 25.

† Heidenhain, 'Pflüg. A.,' v, p. 309.

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* Runeberg, 'Arch. d. Heilk.,' xviii, p. 1.

† Heidenhain, in Hermann's 'Hdb. d. Physiol.,' v, 1, p. 368; Gottwalt, 'Zeitschr. f. phys. Chem.,' iv, p. 423.

Runeberg's series of experiments teaches at least what reserve must be maintained in drawing conclusions with regard to the transudation from the capillaries of the living body from the behaviour of dead animal membranes. For precisely the same relation as obtains for solutions of albumen was determined by Runeberg to hold good of finely-divided bodies in suspension, the intestine being the less permeable to the latter the higher the pressure it has to sustain. Of transudation due to stagnation you know, however, *that it is poorer in albumen than normal lymph, and, on the other hand, considerably richer in suspended constituents,* i. e. *blood-corpuscles.* Hence it follows that, as already stated, we are not yet in a position to propound a mechanical theory of the œdema of stagnation, and that *the aid of unknown influences proceeding from the living vessel wall* must be called in for its interpretation. Thus though venous stagnation has repeatedly been made the subject of experiment as well as of pathological observation, the facts alone are indubitably established. We know that in stagnation an increased amount of fluid transudes; we know further that this fluid is *poor in albumen and in colourless corpuscles,* and therefore *little disposed to coagulate;* and that, on the other hand, the red corpuscles met with in mechanical œdema are *more abundant* in proportion as the venous efflux is impeded.

While even for mechanical dropsy we are compelled to assume a peculiar influence exerted by the vessel wall, this latter acquires a still greater importance in all the remaining varieties of hydrops, by whatever names they are known. It has already been shown that, of the various properties of the vessel wall which must be considered in discussing the relations between it and the circulating blood, it is the *porousness* or *permeability,* on whose alteration or augmentation the increase of the transudation depends; while at the same time special attention was directed to the fact that we have almost without exception to deal in these cases with processes occurring in the capillaries and small veins. There can therefore be no doubt that here also the condition of the *endothelium* is the essentially determining factor. The endothelial membrane is the proper filter between the blood and the surrounding tissue or cavity; this it is that, despite its extraordinary thinness and delicacy, suffices in normal conditions to confine not only the corpuscular constituents of the blood, but the greater part of the dissolved albumen as well. Since, however, the endothelium is a true *animal membrane* the laws applying to filtration through animal membranes hold good of it; and it perfectly accords with this that, as compared with the blood-serum, the composition and amount of the salts passing over into the transudations remain approximately the same, while the albuminous contents of the transudations is under all circumstances reduced. Moreover, I stated a moment since that the new principles established by Runeberg admit in part of a direct application to the capillary membrane. Yet, as you no doubt noticed, in part only. For the endothelium of a vessel is, on the other hand, a *living tissue*, or, if you prefer it, *organ*, with a metabolism which, though quite unknown to us, is certainly very active. We are unable to give its chemical composition with exactness, to say nothing of the processes by which its normal constitution is maintained. We cannot do more than describe the *conditions* which must be fulfilled in order that it may remain intact. The most important of these is the bathing of the endothelium by the normal blood-stream, *i. e.* the blood must not depart to any considerable extent from the normal standard, either in composition, amount, velocity, or temperature. Hence so soon as the blood or lymph contains substances chemically foreign to it which come into contact with the endothelium, so soon as the temperature becomes fully abnormal, so soon as the albuminous contents of the blood grow abnormally small, so soon as the oxygen contents of the blood fall through any cause below the normal, or so soon as considerable local disturbances of the circulation, such as extreme ischæmia, pronounced venous stagnation, have become established in the vascular area—we must in all these cases expect sooner or later a reaction on the part of the endothelium. The rapidity and vigour of this reaction depends partly on the degree of severity and permanency of the noxæ to which the endothelium is exposed, and partly on its sensibility, or, if you prefer it, irritability,—a property that, as you are well aware, differs in different vessels. But though we are not in a position to specify the precise alterations called forth in the endothelium by the individual noxæ, we are acquainted with some of the *functional disturbances* attending these alterations. The permeability is one of the functions concerned; and this, if affected at all, apparently suffers an *augmentation* as the effect of each of these noxæ. There is first an increase of permeability to *dissolved albumen* and then to the *corpuscular elements* of the blood. There unquestionably occurs a gradual ascent from the former to the latter, *i. e.* in the slighter degrees we find the transudation consisting of an increased amount of an albuminous solution with an abnormally high percentage contents, while in more pronounced cases the corpuscles also transude. The proportion of the corpuscles to the serum in the transudation may depend on still other conditions—on whether *e. g.* the adhesion of the vessel wall with the blood, *i. e.* the frictional resistance, has increased at the same time with the permeability, and thus given rise to pavementing and stagnation of the blood-corpuscles, but it is also possible that particular noxæ are attended by particular disturbances of transudation. I referred a short time since to factors which make it not improbable that the impoverishment of the blood in oxygen-carriers, or the defective function of these, increases the permeability of the capillary walls to red blood-corpuscles (p. 396).

That we are still so far removed from an actual comprehension of all these processes will be matter for regret most of all to those who are fully sensible of their extreme frequency and importance. Chief amongst them, I need hardly say, is the true *inflammatory œdema;* indeed it occupies such a predominant position in this class of dropsies that it appears not unjustifiable to name the entire category after it. I have in fact already (p. 323) called attention to the so-called *collateral œdema* as being nothing more or less than an inflammatory one, and shown that the same applies to *œdema glottidis*, to many forms of *hydrocele*, of *hydrocephalus*, &c. But the notion of a hydrops inflammatorius admits of much further extension. The *œdema of the skin* occurring in persons suffering from trichinosis, in the neighbourhood of the infected muscles, depends neither on lymph-thrombosis, as Klob* supposed, nor on the destruction of the capillaries of the muscles, as Colberg* believed, but is simply of *inflammatory* origin. The so-called hydrops irritativus, produced by slight irritations in persons with a very sensitive skin, the remarkable cases of acute anasarca clearly traceable to *exposure to cold,* the so-called œdema *ex vacuo,* the articular dropsy of the knee that sets in on again moving the joint after the limb has long remained at rest in an extended position, are all œdemas due to augmented permeability of the vessels, and are consequently inflammatory œdemas. The common elements in all these œdemas have long been known to you, and I have moreover just now reiterated them to a superfluous extent. They are the *relatively high albuminous contents* of the œdematous fluid, and *its contents in blood-corpuscles, more especially colourless ones;* with respect to the last of which, it is true, very considerable variations are found; so much so that in many of these dropsies extremely few white cells are present, while in others these closely approach in number the leucocytes of fibrinous exudations. The dropsical fluid will of course be clearer or more turbid in proportion as the quantity of lymph-corpuscles is smaller or larger; and if an extensive fatty degeneration and disintegration of the corpuscular elements takes place in addition, the fluid may become quite opaque and milky, and so acquire a deceptive resemblance to true chylous ascites or hydrothorax, *i. e.* to an accumulation of fluid due to the effusion of chyle into either of the cavities in question.† From former lectures you are quite familiar with the fact that the tendency to coagulation increases *pari passu* with the number of leucocytes. Accordingly we should possess in the constitution of the dropsical fluid an excellent criterion for the differential diagnosis between inflammatory œdema and the œdema of stagnation were it not that the so-called *cachectic* dropsies introduce a fresh complication into the whole question.

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* Klob, 'Oesterr. med. Jahrb.,' 1866.

This name was long ago conferred on those dropsies which depend, not on a change in the filter- or filtration-pressure, but on an alteration in the third factor necessarily influencing the entire process of filtration, namely, *the constitution of the filtered fluid,* in the present case, the circulating blood. Now,

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* Colberg, 'Deutsche Klinik,' 1864, No. 19.

† Quincke, l. c.; Stern, 'Virch. A.,' lxxxi, p. 384.

I have already sought in another place (p. 453) to restrict the notion of *hydræmic œdema* to its proper limits. Were the capillary wall in reality a simple animal membrane, merely obeying the laws of filtration and diffusion, one would of course be fully justified in anticipating an augmentation of the transudation on the albuminous contents of the blood-serum becoming diminished. On this point all writers are agreed; and Runeberg could but confirm the fact that solutions of albumen filter more readily through animal membranes the less concentrated they are. But this is altogether inapplicable to the normal capillary wall. The blood may be diluted till its dry residue is reduced one half, indeed a much weaker solution of albumen may be conveyed through the vessels of a rabbit's ear, without a trace of œdema or the least increase in the lymph-stream. A change takes place, as you will remember, only when the permeability of the vessel walls becomes abnormal, is increased. To what cause this pathological increase of permeability is due is not relevant to the point now under discussion; but I may remind you that, *e. g.* in the anasarca of nephritic persons, the dropsy is very often preceded by unmistakable inflammatory affections of the skin. It is, however, especially noteworthy that *the hydræmic quality of the blood is itself such a factor, and will, if persistent any length of time, increase the permeability of the vessel walls.* I recently made you acquainted with the experiments and experiences bearing out this conclusion; and I should not now recur to the subject did I not wish to state most emphatically that this fact allows of our still maintaining the category of cachectic œdema. Please bear in mind, however, that the *hypalbuminosis though the remote, is not the proximate cause,* of this form of dropsy; that the latter is directly dependent on an alteration in the vessel wall; and is therefore, if you accept the proposition I formerly made, an inflammatory hydrops, yet, certainly, with a fluid differing absolutely from that of all other inflammatory œdemas. For since an abnormally weak solution of albumen circulates through the vessels, a large quantity of fluid will transude, but the albuminous contents will be very small; and if no other grounds for an extravasation of corpuscles exist, the œdema will also be very *poor in corpuscular* *elements.* The fluid of cachectic œdema has accordingly a much closer resemblance to that of mechanical than to that of inflammatory hydrops, despite the fact that genetically it is much more closely allied to the latter than it is to the dropsy due to stagnation.

I have now, I believe, adduced all the factors which will enable you, if you attend to them, to form a correct opinion of any dropsy you may chance to meet with. The constitution of the œdematous fluid will in many cases lead to a certain decision; but the essential point will always be the consideration of the case in its entirety with a view to discover the cause of the hydrops. By making this a rule you will run no risk of mistaking the nature of a dropsy even when it is the effect of more than one cause; for if thrombosis occurs in a hydræmic subject or inflammation sets in in the œdematous extremity of a person suffering from cardiac disease, the characters of the œdematous fluid must certainly greatly depart from those of the typical transudation of stagnation. Such complications may greatly enhance the difficulty of judging individual cases, they may obscure or obliterate the entire picture; nevertheless the categories of dropsy previously marked out are not thereby affected. Nor, on the other hand, must we allow ourselves to be led by such cases into believing that there are no œdemas but those depending on the causes already mentioned. The question of the existence or non-existence of *purely nervous œdemas* has frequently been raised; whether *i. e.* œdema can be directly caused by nervous changes, either by the intensified action of certain nerves, or by the weakening or abeyance of certain nervous influences. Pathology affords us some grounds for such an assumption. The rosy patches in so-called *erythema nodosum*,* and more especially the *wheals of urticaria* may be appropriately cited in evidence; for their development is often incredibly rapid and unattended by any antecedent disturbance of the circulation, and they not uncommonly ensue on undoubted nervous influences, *e. g.* emotional disturbance. These wheals have not, so far as I know, been examined microscopically, but the dimensions of the swelling and its doughy consistence scarcely leave it doubtful that there is present here not only considerable arterial congestion but in addition an accumulation of fluid in the tissues outside the vessels. While then in this case a nervous excitation resulting in a rapid augmentation of transudation suggests itself as the cause, the œdemas occurring in paralysed limbs in disease of the central nervous system are believed to be due to a falling off in the vascular innervation. It is true that the œdemas observed in paralysed extremities are usually no more than slight swellings around the ankles, &c.; and we shall scarcely err in regarding them as simply the effects of that moderate venous stagnation which, owing to the absence of muscular movements, is inseparable from every paralysis. If in patients of this class you meet with anasarca of the leg exceeding to a marked degree such slight stagnative, or, more accurately, *hypostatic* œdema, you may as a rule assume that thrombosis of the principal veins has occurred. Yet these considerations do not meet the case of those considerable œdemas which, according to the statements of reliable clinicians,* develop very rapidly in the extremities in isolated cases of acute myelitis, the efflux of venous blood being unimpeded by thrombi. Taking these results in connection with the oft-mentioned experiment of Ostroumoff—production of œdema of the tongue by irritating the lingual nerve—and again with the observation of Gergens that frogs whose spinal cord has been destroyed become œdematous under conditions where animals having the cord intact are not so affected, it will be seen that the assumption of a direct and immediate influence exerted by the nerves on the process of transudation has much to support it. A dropsy originating in this way would undoubtedly be placed by us in that category of œdemas which depends upon alterations in the constitution of the vessel walls; for I cannot conceive how the nerves could directly augment the transudation except it were by increasing the permeability of the vessel walls. Nevertheless, we shall do well to wait a little before committing ourselves to this view, however general, and little calculated to give rise to error, it may be. For it must be borne in mind that we are now speaking of experiences and observations which still require thorough scientific investigation, and that the materials for a possible future doctrine of "nervous hydrops" are at present extremely fragmentary.

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* Cf. Lewin, 'Neue Charité-Annalen,' iii, p. 622.

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* Leyden, 'Klinik der Rückenmarkskrankheiten,' ii, p. 173.

We occupy a much more favorable position to-day with regard to another form of œdema—one that till recently appeared to hold a perfectly isolated position amongst all remaining forms, and that, in point of frequency and more especially significance for the organism, is perhaps the most important of all—I refer to *pulmonary œdema.* Not as though œdema of the lung in every case eluded explanation. It was apparent to everyone that an œdema, involving the upper half of the inferior lobe of a lung, the lower half of which was hepatised, or one developed in the neighbourhood of a pulmonary abscess, was *in optima forma* inflammatory. But there are in addition other, if I may say so, *independent* varieties of œdema of the lung. As is well known, pulmonary œdema very frequently sets in during the agony, not merely in nephritis and heart affections, but in all possible diseases, carcinoma, spinal lesions, &c.; and on referring to the records of autopsies of persons who have succumbed to various chronic complaints you will find "pulmonary œdema" set down as the immediate cause of death in an extremely large proportion of cases. Still more interesting are the *attacks of pulmonary œdema,* mostly violent in their development, to which patients suffering from some general disturbance of the circulation are peculiarly liable. The seizure is either sudden, or preceded by trifling premonitory symptoms; the patient having previously been free from any symptoms of a severe or threatening character. There was never it is true, any dearth of hypotheses purporting to explain this dangerous variety of pulmonary œdema. It was more particularly attributed to rise of pressure in the pulmonary capillaries; and since the fact, so repeatedly noticed, that dogs often perish through severe œdema of the lung, as the result of the injection of oil or finely divided particles into the v. jugularis, was referred by Virchow* to the action of excessive pressure in the vessels behind the obstruction, the belief in arterial congestion, equally with venous stagnation, as a cause of œdema in the lungs has become quite generally prevalent.

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* Virchow, his 'Archiv,' v, p. 308.

In the lungs, nevertheless, it may be most strikingly demonstrated that augmentation of arterial pressure *never* causes œdema in them. For when in the rabbit or dog a ligature is applied to the left main division of the a. pulmonalis and also to the arterial branches distributed to the superior lobe of the right lung; or when as much as three fourths the total sectional area of the arteries is occluded by emboli, and the animal survives, œdema never arises in the pulmonary tissue supplied by the remaining arteries. On the other hand, every stenosis of the left auriculo-ventricular opening most plainly shows that the mere impeding of the venous efflux from the lungs is far from being sufficient in itself to give rise to transudation and œdema. Nor could it make any essential difference were the engorgement, which is supposed to ensue, called forth by a weak heart. If *general feebleness of the heart* were really the cause of pulmonary œdema, as has often been assumed, more especially by clinicians, it should attend every profound syncope; indeed the very large majority of human beings should die from pulmonary œdema: but this is far from being the case. For this reason—because in conditions appearing to be absolutely identical the affection is by no means constant in its occurrence—the entire question of hydrops pulmonum is made more complicated. In some individuals dying of a chronic affection, loud *râles* develop during the agony over a large portion of both lungs, a reddish froth may rise into the mouth and nose, and a considerable quantity of fluid be expressed from the lungs at the autopsy; in other examples of the same disease, on the contrary, though the agony have lasted equally long, the lungs remain quite dry. The results are similar after experimental interference of the most varied kinds, *e. g.* after artificial oil-, or analogous, embolism; and this whether the pulmonary capillaries are occluded slowly and gradually or in rapid succession: by far the greater number of animals die from simple asphyxia. Further, Pokrowsky* observed pulmonary œdema in some of his rabbits and guinea-pigs after making them breathe carbonic oxide, while œdema of the lung is far from being the usual cause of death in persons poisoned by inhaling the fumes of charcoal. Call to mind, lastly, how injection of salt solution produced a fatal pulmonary œdema in individual animals, though in the remainder the lungs remained absolutely dry. Does not this striking inconstancy seem to make against the view that the œdema of the lung is due to purely mechanical factors in these cases? And yet anyone who has even once witnessed one of those violent attacks of pulmonary œdema, common in cardiac disease, and seen that it is neither preceded nor followed (should the paroxysm be happily survived) by the least indication of any abnormal condition of the pulmonary vessels, will certainly reject the idea that he is dealing with a hydrops inflammatorius, *i. e.* one depending on an alteration in the vessel walls.

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* Pokrowsky, 'Virch. A.,' xxx, p. 534.

But, while the albuminous contents of the fluid of the œdema admit no doubt that the latter originates in an abnormally abundant transudation from the blood-vessels, and the constant presence of red blood-corpuscles in large numbers renders it from the outset most probable, despite all that has been said, that the œdema is stagnative, this supposition has been recently raised to a certainty as the result of an investigation carried out by Welch* in my laboratory at Breslau. Setting out from the fact, long known to us, that occlusion of the aorta ascendens in rabbits brings on very rapidly a violent pulmonary œdema, we endeavoured first of all to determine whether stagnation in the pulmonary circulation is capable of causing an œdema, and if so under what conditions. The investigation showed that stagnative œdema sets in only *when the obstacles opposed to the efflux of blood from the pulmonary veins are such as cannot be overcome by the right ventricle.* True, for this much is requisite; you know that the right ventricle can easily overcome the resistance caused by reducing the total sectional area of the pulmonary arteries to one fourth the normal. Hence the closure of the great majority of all the pulmonary veins is also indispensable to the establishment of a fatal pulmonary œdema. The required insuperable obstacle may, however, be secured with still greater certainty and, at any rate, more simply by making it impossible for the left ventricle to receive blood, or to discharge the blood, after it has entered, into the aorta.

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* Welch, 'Virch. A.,' lxxii, p. 375; Cohnheim, 'Stzgsb. d. schles. Ges. f. vaterl. Cult.,' Med. Section, 7 Dec., 1878.

For if either the left auricle or the ventricle itself be compressed by a clamp provided with strong springs, or the aorta ascendens be ligatured, blood will very soon cease to flow from the pulmonary veins; and if the right ventricle now continues to act an enormous stagnative œdema must develop very rapidly, provided the contractions of the right ventricle really send an increasing amount of blood into the pulmonary vessels. For you will doubtless meet me with the question, whence can the right ventricle obtain the blood when the left has ceased to work effectively? In ligature of the a. ascendens it might be supposed that the blood, though small in quantity, conveyed by the coronary veins into the right auricle was the source of supply; yet when the left auricle or ventricle is compressed the coronary arteries receive no blood and still the pulmonary œdema ensues with absolute certainty. The forces here available for the propulsion of the blood through the systemic veins into the right heart can be only, as S. Mayer* has rightly emphasized, accessory ones. Those operative as such are the *suction power of the right ventricle*, together with that of *the entire thorax*, both of which are considerably augmented by the *dyspnœic respiratory movements* that follow close upon the impeding of the blood-stream through the lungs. It is also obvious that these more vigorous respiratory movements must, by increasing the pressure on the contents of the abdominal cavity, tend to propel the blood contained in the abdominal vessels towards the right heart. Moreover, an important part in feeding the right heart is taken by the *tonic contraction of the arteries*, with regard to which it is, you are aware, established that by its means the blood is forced into the veins, and through these into the heart. This particular assumes the greater importance here inasmuch as the cessation of the aortic stream soon brings on cerebral anæmia, which is, as you know, the most effective means of augmenting the arterial tonus. To the foregoing must still be added an excellent aid to the systemic venous stream, namely, the *convulsions* which so readily supervene on cerebral anæmia of acute origin. So weighty a part do these convulsions play in the entire process, at least in the rabbit, that S. Mayer found the pulmonary œdema absent in curarised animals under conditions where in the non-paralysed it invariably set in.

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* S. Mayer, 'Wien. akad. Stzb.,' 3 Abth., 1878, Mai-Heft.

In now applying these experimental results to human pathology it is of course self-evident that the occurrence during life of anything analogous to the above-mentioned operative procedures is altogether out of the question; I cannot imagine in what circumstances an occlusion of the majority of the pulmonary veins, a compression of the left auricle or ventricle, or a closure of the ascending aorta could occur. Whether a continued tetanic contraction of the left ventricle (which obviously would be attended by the same effects) has ever been observed is more than doubtful. Still there exist two conditions, thoroughly adapted to produce the required insurmountable resistance to the escape of blood from the pulmonary veins; in the first place *a rise of arterial blood-pressure so enormous* that the ventricle, exerting itself to the utmost, is helpless against it; and, in the second place, a *direct feebleness, paralysis, of the left heart-muscle.* Both evidently amount to the same thing at bottom, namely, exhaustion of the left ventricle, though in the latter case the exhaustion is primary and to a certain extent absolute, while in the former it is, on the contrary, secondary and relative. For if we speak of the functional power of the heart as sufficient or insufficient, we do so having regard to its relation to the resistances to be overcome, and a moment's reflection will show what an intimate interdependence there is between these two factors. A rise of arterial pressure so great as to be insuperable by the left ventricle must of necessity quickly bring about its complete exhaustion, if for no other reason, because the coronary arteries no longer receive their regular supply of blood. But this is not all; for I pointed out a moment ago that feebleness of the left heart of acute origin will, by causing cerebral anæmia, of itself give rise to tetanic contraction of the small arteries with elevation of arterial pressure. From this close connection it will also be clear how it is that the left ventricle may, as the result of *general* weak heart, become much more rapidly paralysed than does the right; it needs but a slight increase of the resistances to completely exhaust the enfeebled ventricle, and this the cerebral anæmia accomplishes, in so far at least as the vaso-constrictors are still capable of excitation. I need hardly point out that the danger of rapid paralysis of the left heart-muscle is greatest in all cases where, as the result of some pathological condition or other, the demands on the left ventricle have for a long time been abnormally severe, and therefore very specially, in *cardiac lesions.*

From this standpoint, as it seems to me, we may find a ready explanation not only for the unexpected deaths from pulmonary œdema which occur in so many experiments, but also for the attacks of general pulmonary œdema met with more particularly in cardiac cases. The œdema is here *stagnative*, and occasioned by feebleness of the heart; not, however, by *weakness* of the entire organ, but only and solely *of the left ventricle, while the right continues in action.* Whether the latter act with normal, increased, or diminished power is in principle immaterial, and any change can at most accelerate or retard the development of the stagnation and stagnative œdema; the only essential is that it should continue to act. In lesser degrees of the process, in stagnation which may be said to have only just begun, the entire phenomenon stops short at the expectoration of a pale red material containing minute air-bubbles, preceded by slight râles over the breast,* and is quickly at an end. But even severe attacks, in which nothing is wanting to complete the picture of highly dangerous pulmonary œdema, may terminate favorably if the heart recover itself, either spontaneously or on stimulation. During the paroxysm, the radial pulse becomes, despite the threatening asphyxia, small and even imperceptible to the finger,—an occurrence which on our view is comprehensible enough. Should, however, the attack have a fatal termination, the right heart is found after death over-filled with blood and greatly distended, the very natural consequence of the fatal pulmonary stagnation.

To the opinion that occlusion of the *a. coronaria sin.* in man is followed by acute paralysis involving the left heart-muscle alone, and hence by stagnative œdema of the lungs, I am not disposed to subscribe without further investigation, although Samuelson† draws this inference from experiments on the compression of the coronary arteries in rabbits. For, to say nothing of how very questionable it is whether spasm of the coronary arteries ever occurs with sufficient energy to cause complete occlusion of the lumen for a period of some minutes—and it is hardly possible that any other kind of occlusion could ever properly come into consideration here—we are warned to observe the most extreme caution in coming to a conclusion by the experiments on the results of ligature of the coronary arteries in dogs, with which I formerly made you acquainted. It is quite true that, *in individual cases* of occlusion of the a. coron. sin. in the rabbit, the left ventricle suffers paralysis earlier than does the right; in the dog, on the contrary, ligature of one of the larger branches even of the coronary arteries is invariably followed after a very brief interval *by complete standstill of both chambers,* so that not even a trace of pulmonary œdema is ever developed. How does Samuelson know whether the human heart more closely resembles in this respect that of the rabbit or that of the dog?

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* Cf. Traube, 'Ges. Abhdl.,' iii, p. 287.

† Samuelson, 'Med. Ctbl.,' 1880, No. 12; 'Zeitschr. f. klin. Med.,' ii, p. 12.

If he be right, the view developed by us will all the more completely explain the so-called *final pulmonary œdema.* For this also is nothing but a stagnative œdema caused by the earlier paralysis of the left ventricle. That the right heart of a moribund person ceases beating later than does the left was known as early as the time of Haller, and this, in all probability, depends on the fact that the left ventricle, with its more powerful muscle, reacts much sooner than the right to a deficient supply of oxygen, and consequently to imperfectly aerated blood.* If this be the case, the final pulmonary œdema is not so much the cause of death as the effect of the agony: *a man does not die because he gets œdema of the lung, but he gets œdema of the lung because he is on the point of dying.*†

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* S. Mayer, 'Prag. med. Woch.,' 1880, No. 14.

† On the subject of dropsy, &c. consult also Virchow, 'Hdb.,' i, p. 182; O. Weber, in Pitha-Billroth's 'Hdb.,' ii, Abth. 2, p. 63; Lebert, in Virchow's 'Hdb.,' v, Abth. 3, p. 124; Ludwig, 'Oesterr. med. Jhrb.,' 1863, xix, p. 35.

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